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MECKEL'S DIVERTICULUM CONTAINING ABERRANT PANCREAS

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LOS ANGELES

The condition of aberrant or accessory pancreas was first described by Klob in 1859. In 1860 Montgomery cited a case which was recorded by Bristowe in his book of necropsies in 1851, in which a pancreatic nodule ¾ in. (1.9 cm.) in diameter and ⅓ in. (0.83 cm.) thick was found in the wall of the ileum. The nodule was in the middle of the ileum and was lobulated in appearance. As early as 1727 Jean Schultz reported a case which, although it is not authentic, as there is no proof that the nodule found was pancreatic, is interesting from a historical standpoint. He wrote that he found at autopsy in a new-born child "a wart similar to a gland" in the apex of a cone-shaped diverticulum of the ileum. The diverticulum was 4 cm. long and was situated 10 cm. from the ileocecal valve.

Aberrant or accessory pancreas is an infrequent anomaly. Opie found 10 cases in 1,800 autopsies, and Horgan found 2 cases in 314 autopsies. Since Klob reported his case there have been approximately 186 instances of aberrant or accessory pancreas recorded. Warthin, in 1904, analyzed 47 previously reported cases and added 2 of his own. Horgan, in 1921, gathered together 32 additional cases from the literature and added 2 of his own, bringing the total of reported instances to 83. The last complete survey of the literature was made by Simpson in 1927. He collected 66 additional cases from the literature and added 1 of his own, making a total of 150 cases of accessory pancreas recorded in the literature. In the course of a review of the literature we found 36 additional cases recorded. Among these were 6 cases of pancreatic tissue in a diverticulum of the ileum, which had been reported earlier than 1927 but were not included by Simpson in his survey—1 of pancreatic tissue in a Meckel's diverticulum which Kaufmann mentioned having seen in the Baseler Museum, another of pancreatic tissue in Meckel's diverticulum, reported in 1928 by Schaetz, and 4 reported in 1904 by Schmauser and Heller and referred to by Bize. Since Simpson's publication in 1927, 29 additional cases of aberrant pancreas have been reported, in which the diagnosis was corroborated by microscopic section. In only 1 of these was the aberrant pancreas located in a

Meckel's diverticulum. The literature, as we have been able to review it, contains the reports of approximately 186 cases of aberrant or accessory pancreas. In 33 cases the aberrant pancreas existed in a diverticulum of the stomach, duodenum, jejunum or ileum, and in only 13 of these was the diverticulum described as a true Meckel's diverticulum. Our case of Meckel's diverticulum containing an accessory pancreas, herein reported and added to the literature, we believe to be the fourteenth recorded case.

TABLE 1.—*Cases of Accessory Pancreas Recorded in the Literature Since Simpson's Review in 1927*

	Locations of Accessory Pancreas						
Name of Recorder	Stomach	Duodenum	Gallbladder	Jejunum	Ileum	Meckel's Diverticulum	Total
Alessandri	..	1	..	..	..	..	1
Barcaroli	1	..	..	..	..	..	1
Cafritz	..	1	..	..	..	..	1
Cave	..	1	..	..	..	..	1
Cogniauz	2	3	1	1	..	1	8
Cox	1	..	..	..	..	..	1
de Gaetani	..	1	..	..	..	..	1
Haas	1	..	..	..	..	..	1
Hilarowicz	1	..	..	..	..	..	1
Kaufmann *	..	..	..	..	..	1	1
Lordy	..	1	..	..	..	..	1
Moore	..	..	..	1	..	..	1
Schaetz *	..	1	..	..	..	1	2
Schmauser *	..	..	..	..	4	..	4
Semsroth	..	1	..	..	..	..	1
Ssokolow	..	1	..	..	..	..	1
Sussi	1	..	..	1	..	..	2
del Valle and Brachetto-Brian	1	..	..	..	..	..	1
Vandendorpe	1	1	..	..	..	..	2
Weeks and Steinke	..	1	..	..	..	..	1
Wigrsussi	2	..	..	..	..	..	2
Wohlwill	1	..	..	..	..	..	1
Total	12	13	1	3	4	3	36

* Not included in previous articles but recorded in the literature prior to 1927.

Zenker, in 1861, recorded the first case of a Meckel's diverticulum containing pancreatic tissue. Since that time cases have been reported by Schirmer, Albrecht, Merkel, Hedinger, Kaufmann, Clogg, Nazari, Albrecht and Arzt, Koch and Suzuki, Schaetz and Cogniauz.

Oppel and Horgan completely reviewed the comparative anatomy and embroyology of the pancreas and found that the pancreas is present in every species of Vertebrata from the cyclostomes (the lowest order of fishes) through amphibians, reptiles, birds and mammals to man. The form varies from numerous small and widely scattered glands to the single large gland found in man, and each phase of the embryologic development in man represents in a general way the mature development in the lower Vertebrata.

The anlage of the pancreas usually consists of two separate epithelial buds from the duodenum. The smaller bud arises from the anterior portion of the foregut at the junction of the primitive bile duct and

forms a portion of the head and uncinate process. The larger bud arises from the dorsum of the gut and forms the rest of the head and the body of the gland. These buds grow independently for some time and later coalesce to form the adult pancreas. Occasionally they fuse on both sides of the duodenum and completely encircle it, giving rise to the anomaly known as ring or annular pancreas.

Many theories have been advanced to explain the genesis of an aberrant pancreas. Zenker believed that it is due to an additional bud from the foregut which has developed into a single independent glandular mass, which, as the gut elongates, may be carried a great distance from its point of origin. Glinski believed that it is due to a failure of a primitive anlage to coalesce with the main pancreas. Warthin stated: "It is more probable that accessory pancreatic tissue is formed from lateral budding of the rudimentary pancreatic ducts as they penetrate the intestinal wall, the mass of pancreatic tissue thus formed being snared off and carried by the longitudinal growth of the intestine upward or downward." In Horgan's opinion, the accessory pancreas is formed as a result of the lateral buds of the pancreatic anlage attaching themselves to any organ with which they may be in contact and later being cut off from the main body of the pancreas by the growth and the change of relative position of the two organs.

Anatomically, the aberrant pancreatic nodules are firm yellowish-white irregular masses which vary in size from 2 or 3 mm. to as large as 4 or 5 cm. in diameter. They have been found all the way along the gastro-intestinal tract from the stomach to within a few centimeters of the cecum, as well as in the omentum, mesenteric fat, splenic capsule, gallbladder and umbilical fistula. In 62, or 33 per cent of the 186 reported cases, the nodules were found in the stomach; in 43, or 23 per cent, in the duodenum; in 40, or 21.5 per cent, in the jejunum, and in 30, or 16 per cent, in the ileum. In 178, or 95.7 per cent of the cases reported, the aberrant pancreas was found in the wall of the stomach or small intestine, usually in the muscularis but frequently in the submucous or subserous layer. In 33, or 17.7 per cent of the total series, the aberrant pancreas was in a diverticulum—in 3 cases this was found in the stomach, in 3 others in the duodenum, in 1 in the jejunum and in 26 in the ileum. In 13 cases of diverticulum of the ileum containing aberrant pancreas the diverticulum was reported as a true Meckel's diverticulum.

Histologically the general structure is such that the diagnosis is evident on microscopic examination. The pancreatic acini are usually normal in structure and arrangement and frequently contain granules of zymogen. Islands of Langerhans may or may not be present. In many reports there is no mention made of them; in others they are identified with difficulty, while in still others they are recorded as being

normal in size and number. The ducts, when mentioned, are described as being lined with the epithelium typical of pancreatic ducts and are scattered throughout the acini. They usually coalesce and open into the intestine, although some variations have been noted. According to Opie, they may open into the bile duct; according to Bean and Dreyer, they may occasionally open into the main pancreatic duct. Nicholson stated that they may be continuous with ducts lined by cells identical with those of Brunner's glands. The mucous membrane is usually typical of that portion of the intestine in which the gland is found, but in some cases it has been gastric or duodenal, whatever the location of the nodule. When the accessory pancreas was situated in the muscularis, its growth frequently thinned and separated the muscle fibers to such an extent as to produce a definite weakness in the intestinal wall.

Physiologically, the accessory nodules function like a normal pancreas, and many authors have described granules of zymogen in the acini and ducts filled with richly albuminous precipitate similar to that found in the ducts of a normal gland.

Clinically, it is interesting to note that although the majority of the known cases of accessory pancreas were found at autopsy and had apparently never produced clinical symptoms during life, the remainder had given rise to a large variety of surgical conditions, such as intussusception, in the cases of Brunner, Bize, Benjamin and Hulst; mechanical intestinal obstruction, in the case of Albrecht and Arzt, and in that of Clogg; umbilical fistula, in Wright's case; pyloric and duodenal ulceration, in the cases of Cohen and of Deaver and Reimann; pyloric obstruction, in the case of Hale and in those of Branham; carcinomatous changes, in the cases of Branham, in that of Bookman and in that of Semsroth; pancreatitis, in the case of Mayo Robson, and in those of Opie and Gibson; necrosis of fat, in one of Warthin's cases, and intestinal diverticulum, in the cases of Neumann, Nauwerck, Simon and others. In our case of Meckel's diverticulum containing aberrant pancreas and in that of Thomson the patient complained of symptoms simulating appendicitis. In neither case was the appendix sufficiently involved to account for the symptoms, and in each case the patient was completely relieved after removal of the diverticulum.

REPORT OF CASE

History.—H. J. M., aged 29, a geologist, was admitted to St. Vincent's Hospital on Jan. 31, 1932, complaining of pain in the lower right quadrant of the abdomen. Three days before admission he had suffered an attack of pain in the same region, severe enough to "double him up," which had lasted for two hours. There was nausea but no vomiting. The next morning there were tenderness and rigidity at the site of the pain. That evening he had a similar attack, not so severe as the first but of longer duration. He experienced no radiation of pain, and no urinary

symptoms or intestinal disturbances. Prior to the onset of this illness he had always been in excellent health.

Physical Examination.—The patient was a strong, healthy young man, weighing about 200 pounds (90.7 Kg.). Apparently he was not suffering severe pain. The systolic blood pressure was 112; the diastolic, 78; the temperature was 99.4 F. There were a slight rigidity and considerable tenderness on deep pressure over the lower right quadrant of the abdomen. The remainder of the examination gave negative results. The urine was reported normal except for a few pus cells. A roentgenogram of the kidneys, ureters and bladder showed no unusual condition. Hemoglobin was 70 per cent; leukocytes numbered 13,400, with 26 per cent lymphocytes and 74 per cent polymorphonuclears.

A diagnosis of subsiding subacute appendicitis was made, and appendectomy was advised. The patient was allowed to go home to complete some work, but he had another attack of pain the next day and returned to the hospital. A second physical examination gave the same results as the first, with the exception that the leukocytes had increased to 15,500 and there were 90 per cent polymorphonuclears.

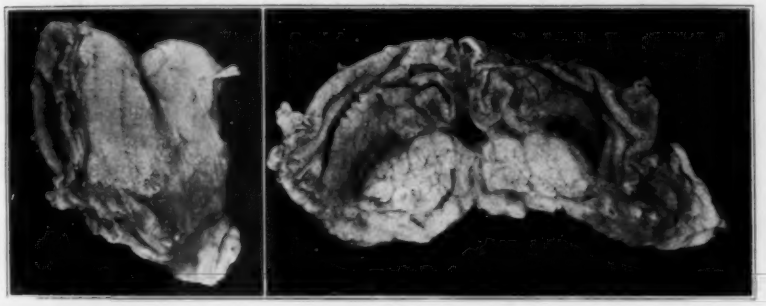

Fig. 1.—Gross appearance of the exterior and interior of a Meckel's diverticulum containing aberrant pancreas.

Operation.—The abdomen was explored on February 1, access being gained through a median right rectus incision. The appendix showed only a moderate amount of inflammatory reaction, which seemed insufficient to account for all the symptoms. Examination of the terminal part of the ileum revealed a Meckel's diverticulum 8 cm. in length, situated about 90 cm. from the ileocecal valve, with what appeared to be a subacute inflammatory process at its tip. The diverticulum and appendix were removed. The stomach, duodenum, gallbladder, right kidney and right ureter were normal. The pathologic examination was made by Dr. E. M. Hall of St. Vincent's Hospital.

Pathologic Examination.—The specimen examined consisted of a Meckel's diverticulum measuring 5 by 3 cm. (fig. 1). At the tip of the sac was a firm polyp-like growth of mucous membrane. The surface of the mucosa over this growth was coarsely granular. In the wall beneath the mucosa was a mass of opaque gray tissue of glandular appearance resembling pancreatic tissue, which measured 2 by 1.5 by 1 cm. In the wall of the diverticulum, forming the sides of the tube, all the layers of the normal bowel could be distinguished. The mucous membrane was rather thick. The muscularis measured about 1 mm. in thickness, and the circular and longitudinal layers could be identified with a hand lens.

Histologic Examination.—Sections of the nodule revealed glandular acini typical of those seen in the pancreas. The lobules were irregular in size and shape and appeared to be somewhat more cut up than in the normal gland. Separating many of the lobules were fasciculi of smooth muscle, indicating that the accessory glandular tissue was intramural. From two to five small islands of Langerhans could be seen in each low power field (fig. 2). These were composed

Fig. 2.—Low power magnification of a section of aberrant pancreas in Meckel's diverticulum, showing small islands of Langerhans.

of cells with extremely clear cytoplasm. Abundant ducts were found in the interlobular fibrous tissue. None of the ducts was dilated, so that it was evident that the secretion reached the lumen of the bowel.

The mucosa covering the accessory pancreas was distinctly hypertrophied. It was of considerable interest also because of its varied constituents. Along one edge of the section appeared fairly normal hypertrophic villi of the small intestine. These were very long and closely set and were covered with thick columnar epithelium having clear cytoplasm. There was a moderate number of rather inactive

goblet cells. The opposite side of the section showed a somewhat similar picture except that the villi were more or less edematous and contained numerous distended goblet cells. A considerable number of round cells and a few eosinophils were present in the supporting connective tissue of the villi (fig. 3).

The mucosa over the midportion of the growth showed the characteristics of gastric mucous membrane. The upper third was composed of short, broad villi

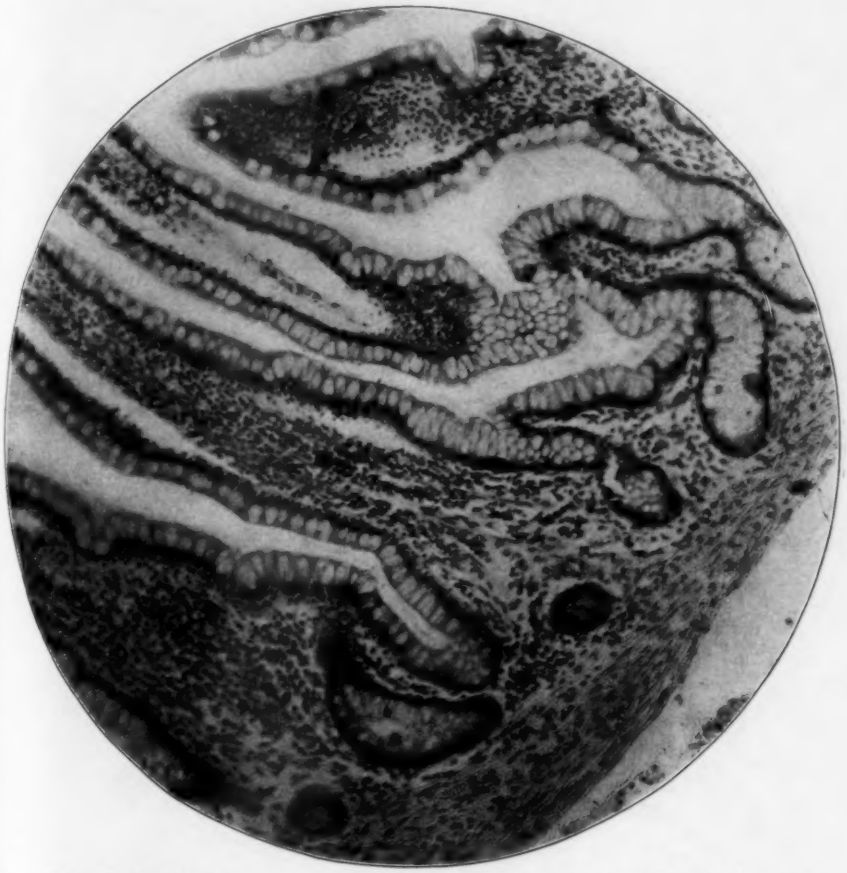

Fig. 3.—Section of mucosa covering an accessory pancreas, in which appear fairly normal hypertrophic villi of the small intestine.

covered with thick epithelium of much the same nature as that described in the preceding paragraph. The deeper two thirds was made up of irregular tubes lined with two kinds of cells: (*a*) a small cell with granular cytoplasm and (*b*) a much larger, plumper cell with bulging sides and clear vacuolated cytoplasm (fig. 4). These types of cells correspond closely with the chief and parietal cells of the gastric mucosa. Many round cells and eosinophils were present in the superficial portions.

Warthin, in 1904, Horgan, in 1921, and Simpson, in 1927, completely reviewed the literature and brought the list of the recorded cases of accessory pancreas up to date at the time of the writing of their respective papers. Table 2 shows the number of cases of accessory pancreas found by previous authors and by us and the locations. The

Fig. 4.—Section of mucosa covering an accessory pancreas, in which are shown chief and parietal cells of gastric mucosa.

discrepancy between the figures of our table and those of Simpson's may be explained by stating that in 6 cases the number of accessory pancreatic nodules was multiple—in 5 cases there were 2 accessory pancreatic nodules, and in 1 case there were 3 nodules. Simpson's table is based on the number of accessory pancreatic nodules, and ours, on the number of cases. The cases listed as occurring in Meckel's diverticula include all conditions claimed by the authors reporting them to be aber-

rant pancreas in a true Meckel's diverticulum, even though the reviewers did not list them as such.

Considerable controversy has arisen among many authors as to whether the diverticula in which the pancreatic nodules were found were secondary diverticula, owing to the presence of the pancreatic nodules, or whether they were true Meckel's diverticula containing accessory pancreases. Opinion is about evenly divided. Kaufmann stated that a true Meckel's diverticulum is located opposite the mesenteric attachment about 1 meter above the ileocecal valve in adults (this may vary from 0.5 to 2 meters at the most) and about from 0.3 to 0.5 meter above the valve in the new-born. The size may vary, but is usually that of a finger. Sometimes the diverticulum has its own mesenteric attachment

TABLE 2.—*Instances of Accessory Pancreas Collected from the Literature*

Location	Warthin (1904)	Horgan (1921)	Simpson (1927)	Hunt and Bonesteel (1932)	Total	Per Cent
Wall of stomach	14	8	25	12	59	31.7
Wall of duodenum	10	4	14	12	40	21.5
Wall of jejunum	13	13	10	3	39	20.9
Wall of ileum	1	1	2	..	4	2.1
Wall of intestine (exact location not given)	1	1	1	..	3	1.6
Diverticulum of stomach	1	..	2	..	3	1.6
Diverticulum of duodenum	..	2	..	1	3	1.6
Diverticulum of jejunum	1	..	..	..	1	0.54
Diverticulum of ileum	2	3	4	4	13	7.0
Meckel's diverticulum	3	1	6	3	13	7.0
Umbilical fistula	1	..	..	..	1	0.54
Mesenteric fat	1	..	..	..	1	0.54
Omentum	1	..	..	..	1	0.54
Splenic capsule	..	1	2	..	3	1.6
Gallbladder	..	..	1	1	2	1.1
Total number of cases	49	34	67	36	186	

with vessels from the omphalomesenteric vessels. According to Keen, Meckel's diverticulum occurs in about 2 per cent of all persons and may be located anywhere from 4 cm. to 4 meters from the ileocecal valve, but usually it is situated between 30 and 90 cm. from the valve. It is generally more than 2 cm. in length, and may have a direct connection with the umbilicus or may be united indirectly with vascular bands to the mesentery, intestines or umbilicus.

Zenker, in 1861, reported that he had found at autopsy in an adult a nodule of pancreas the size of a cherry pit in the fatty tissue around the apex of a true Meckel's diverticulum and communicating with the diverticulum only by means of a small duct. The diverticulum was 54 cm. from the ileocecal valve. He was of the opinion that under the circumstances it would have been impossible for the accessory pancreas to have been a causative factor in the production of the diverticulum. Albrecht and Arzt described a cordlike structure of connective tissue extending from the apex of a diverticulum and containing an accessory

pancreas, which they thought was a remnant of the omphalomesenteric duct and the presence of which they considered as definite proof that the diverticulum was a true Meckel's diverticulum. Koch and Suzuki examined 50 Meckel's diverticula at autopsy and found pancreatic tissue in 2 of them. Wright performed an operation on a child 12 years of age for a congenital umbilical fistula, which he found was due to an accessory pancreas draining through the umbilicus. This suggests that the accessory pancreatic nodules can become disseminated along the omphalomesenteric tract. Furthermore, among others, Schirmer, Eugen Albrecht, Merkel, Hedinger, Kaufmann, Nazari and Cogniauz described cases in which the pancreatic nodule was located in a diverticulum of the ileum, which they considered to be a true Meckel's diverticulum.

Neumann, Brunner, Bize, Simon, Robertson and Hulst reported cases of an accessory pancreas in a diverticulum of the ileum, which diverticulum they believed was the result of the presence of the accessory pancreas. In support of this view they urged that Meckel's diverticulum occurs in a definite location, and that in only a small percentage of the cases was the diverticulum found in such a location that it might be considered a true Meckel's diverticulum; also, that there have been cases in which the diverticulum containing pancreas has been found at any point along the gastro-intestinal tract from the stomach to within a few centimeters of the ileocecal valve. They explained the formation of the diverticulum by stating that a nodule of pancreas located in the musculature of the intestine could so spread and weaken the muscular coat during growth that the intra-intestinal pressure and the peristaltic traction on the nodule would produce a bulging or diverticulum at that particular point. In support of this argument Nauwerck's case was interesting in that two distinct diverticula were found, the proximal one at a distance of 230 cm. and the distal one at a distance of 80 cm. from the ileocecal valve. The proximal diverticulum contained pancreas; the distal one was a true Meckel's diverticulum and did not contain pancreas. The author pointed out the similarity of the two diverticula and stated that had he not found the second one he would have considered the diverticulum containing the pancreas a true Meckel's diverticulum. It is probably true that many of the diverticula containing an accessory pancreas are secondary to the presence of the accessory pancreas in the gastro-intestinal wall; however, as is fairly well proved by the cases reported by Wright, Albrecht and Arzt, Clogg, Koch and Suzuki and others, accessory pancreatic nodules may be disseminated along the omphalomesenteric duct and may be found in direct association with a true Meckel's diverticulum.

SUMMARY

The literature contains reports of 186 cases of accessory or aberrant pancreas; in 178 cases the aberrant pancreas was found in the stomach, duodenum, jejunum or ileum. For the most part the aberrant pancreas existed as a nodule in the normal gastro-intestinal wall. In 33 cases, however, it was found in a diverticulum of the stomach, duodenum, jejunum or ileum. In only 13 of these cases was the diverticulum classed as a true Meckel's diverticulum. The case herein reported is the fourteenth recorded case of a true Meckel's diverticulum containing pancreatic tissue.

RECORDED CASES OF DIVERTICULUM OF THE TERMINAL ILEUM CONTAINING ABERRANT PANCREAS

The situation of the diverticulum in the cases reported ranged from 10 cm. to 2.3 meters from the ileocecal valve. They may be cases of true Meckel's diverticulum but were not designated as such by the authors.

CASE 1.—Neumann, in 1870, found at autopsy in a boy, aged 10 months, a diverticulum 60 cm. above the ileocecal valve, to the apex of which an accessory pancreas the size of a pea was attached by a pedicle.

CASE 2.—Nauwerck, in 1892, found in a man, 43 years of age, a diverticulum 9 cm. long, located 2.3 meters above the ileocecal valve, in the apex of which there was an accessory pancreas. Another diverticulum which was found in the same patient, 80 cm. above the ileocecal valve, Nauwerck considered a true Meckel's diverticulum. The latter contained no pancreatic tissue.

CASE 3.—Brunner, in 1899, found at operation in a child, aged 4½, an intestinal obstruction resulting from the invagination of a diverticulum into the lumen of the ileum. The diverticulum was situated 37 cm. above the ileocecal valve and contained in its apex an accessory pancreas 22 mm. in diameter. Brunner was doubtful whether this was a true Meckel's diverticulum.

CASES 4 and 5.—Bize, in 1904, cited a case of Bize and Kirmisson, who had observed at autopsy following an operation for intussusception a diverticulum the size of the thumb, 25 cm. from the cecum, which contained a nodule of pancreas the size of a hazelnut.

Bize cited another case, of Bize and Grisel, in which was found at operation in a child, 6 years of age, a diverticulum 4.5 cm. long, situated 60 cm. from the ileocecal valve. The diverticulum was invaginated into the lumen of the ileum and contained in its apex an accessory pancreas the size of an almond.

CASE 6.—Simon, in 1905, found a diverticulum the size of a thumb 75 cm. above the ileocecal valve, in the apex of which there was an accessory pancreas.

CASE 7.—Thomson, in 1908, found at operation in a man, aged 33, a diverticulum 45 cm. above the ileocecal valve, which contained an accessory pancreas in its tip.

CASE 8.—Hulst, in 1909, found a polyp-like structure 2.5 cm. long, situated 10 cm. above the ileocecal valve, containing at its apex an aberrant pancreas 12 mm. in diameter. This structure represented an invagination of the intestinal wall. The author was doubtful as to whether or not it was a true Meckel's diverticulum.

RECORDED CASES OF TRUE MECKEL'S DIVERTICULUM CONTAINING ABERRANT PANCREAS

CASE 1.—Zenker, in 1861, found at autopsy in an adult a true Meckel's diverticulum. The diverticulum was shaped like a "finger of a glove." Embedded in the fatty tissue near its apex was an accessory pancreas.

CASE 2.—Schirmer, in 1893, found at autopsy in a boy, 3 years of age, a true Meckel's diverticulum shaped like a "finger of a glove." It was located 115 cm. from the ileocecal valve on the convex margin of the ileum and measured 8 cm. in length and 2.5 cm. in diameter; it had a small mesentery of its own. In the apex of the diverticulum was a small nodule of accessory pancreas the size of a bean.

CASE 3.—Albrecht, in 1901, found a true Meckel's diverticulum with a nodule of aberrant pancreas in its apex.

CASE 4.—Merkel, in 1905, found at autopsy a true Meckel's diverticulum 1.5 meters from the ileocecal valve, in the apex of which he found a "pancreatic embryo."

CASE 5.—Hedinger, in 1906, found at autopsy in a man, 36 years of age, who had died of heart trouble, a true Meckel's diverticulum 5 cm. long and located about 1 meter above the ileocecal valve on the convex surface of the intestine, in the apex of which he found a nodule of pancreas 2.5 by 0.5 cm. in diameter.

CASE 6.—Kaufmann, in 1907, reported a case in the Baseler Museum in which an accessory pancreas the size of a nut was found in the tip of a diverticulum located at the site corresponding to the location of a true Meckel's diverticulum.

CASE 7.—Clogg, in 1908, found at operation in a boy, 12 years of age, in whom symptoms of intestinal obstruction had developed immediately following a blow in the abdomen, a true Meckel's diverticulum ¾ in. (1.9 cm.) in length, in the end of which was a flat mass of pancreatic tissue ¾ in. in diameter.

CASE 8.—Nazari, in 1909, found at autopsy in a man, aged 35, who had died of hemorhage following perforation of a gastric ulcer, a true Meckel's diverticulum 5 cm. long and 1 cm. in width, located 1 meter above the ileocecal valve, in the apex of which there was a mass of pancreatic tissue 1 cm. in diameter.

CASE 9.—Albrecht and Arzt, in 1910, reported the case of a boy, 15 years of age, who had always had good health until three days before operation, when he was seized with pain resembling colic, which gradually increased, with the development of complete obstruction, fecal vomiting and visible peristalsis. At operation the intestine was found to be greatly distended and inflamed, and the abdomen contained turbid fluid. The obstruction was found to be due to a very tightly stretched cord of connective tissue, which was severed. One end of the cord was attached to the apex of a Meckel's diverticulum which contained an accessory pancreas. The attachment of the other end of the cord could not be found. Albrecht and Arzt believed this cord to be a remnant of the omphalomesenteric duct and were of the opinion that its presence was conclusive evidence that the diverticulum was a true Meckel's diverticulum.

CASES 10 and 11.—Koch and Suzuki, in 1912, examined 50 Meckel's diverticula at autopsy, in 2 of which they found accessory pancreatic tissue.

CASE 12.—Schaetz, in 1925, reported a case of Meckel's diverticulum containing pancreatic tissue in a girl, aged 27, who had died of pulmonary tuberculosis. Pancreatic tissue and the gastric type of mucous membrane were found in the diverticulum.

CASE 13.—Cogniauz, in 1928, found at operation for intussusception in a child, aged 4, an invaginated Meckel's diverticulum the apex of which contained an aberrant pancreas the size of a hazelnut.

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MECKEL'S DIVERTICULUM

REPORT OF A CASE OF HEMORRHAGE IN THE BOWEL ASSOCIATED WITH A MECKEL'S DIVERTICULUM THAT PRESENTED AN ADENOMA COMPOSED OF GASTRIC AND DUODENAL GLANDS

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The case reported in this paper is of interest not only because it appears to be unique but also because it emphasizes two aspects of Meckel's diverticulum which have received some attention but are not yet sufficiently appreciated or emphasized. These considerations are, first, that Meckel's diverticulum rather frequently contains heterotopic alimentary tissue, and second, that the diverticulum may manifest itself clinically by bleeding, especially if it contains heterotopic gastric tissue, although this is not the only cause of bleeding. An analysis of the reported cases of bleeding Meckel's diverticulum with a discussion of the more probable causes of the hemorrhage will be given subsequently.

REPORT OF CASE [1]

History.—A boy, aged 16, American born, a high school student, had been in good health up to the onset of the illness to be described, with the exception of mild but persistent constipation associated with occasional vague, transitory pain in the upper part of the abdomen, during the past four years. While attending an exhibition on the afternoon of Nov. 30, 1929, he suddenly felt nauseated and went to a nearby drugstore, where he took some sodium bicarbonate, which he promptly vomited. At this time he felt a desire to defecate and had one small, but well formed, brown stool. On his way home he vomited four or five times and also experienced cramplike pain in the right side of his abdomen, which at first was constant, but later became intermittent, more severe, and finally paroxysmal. On his arrival at home he was taken with diarrhea. The first stools were watery, but these were soon followed by large bloody movements in which there was a small amount of mucus with bright red blood but not mixed with the blood. There was no history of a preceding dietary indiscretion. The family physician found the patient acutely ill and pale, with a pulse rate of 140 and a subnormal temperature. The extremities were cold, and the patient seemed to be in a state of shock. Hospitalization was advised, and he was immediately brought to the Presbyterian Hospital and admitted to the first surgical division.

From the Surgical Service of the Presbyterian Hospital and the Laboratory of Surgical Pathology of the College of Physicians and Surgeons, Columbia University.

1. This case was presented before the Section of Surgery, New York Academy of Medicine, Oct. 3, 1930.

Examination.—When first seen by one of us (R. N. S.), the patient was tall and rather thin for his age, and seemed acutely ill and in evident pain. His face was flushed. The pulse rate was 120; the blood pressure, 80 systolic and 60 diastolic, and the temperature, 103 F. by rectum; respirations were 28 per minute and entirely thoracic. The throat was slightly injected, and the heart, except for its rapid rate, was normal; the lungs were clear. The abdomen was scaphoid and symmetrical and presented no scars or rash. It did not move with respiration, and no peristaltic waves were noted. There was involuntary spasm over the whole right lower quadrant with associated tenderness. The point of maximum tenderness was slightly above and mesial to McBurney's point. Rebound tenderness was present over this same area, but no mass could be felt. Fluid wave, areas of shifting dulness and obliteration of liver dulness were absent. The rectal ampulla was empty, and no mass could be felt in the lumen above or impinging on the rectal wall. There was slight tenderness high up on the right side of the rectum. During the examination the patient had three very severe paroxysms of pain lasting about three minutes, then gradually subsiding. There was also one large bowel movement consisting of bright red blood *unmixed* with mucus. The red cell count was 4,700,000 and the white cell count 16,500 with 93 per cent polymorphonuclears. Urinalysis gave negative results.

The picture was unusual. There was nothing in the past history to suggest duodenal ulcer. The severe pain and prostration, with the signs pointing to the ileocecal region, suggested an intussusception, but in this condition bloody stools are supposed to occur only once or twice and in smaller amounts, while the blood is said to be *mixed* with the mucus. Volvulus was considered as another possibility, as well as a bleeding ulcerated intestinal polyp or perhaps an ulcer of the lower portion of the ileum or of the cecum. Acute colitis and the various dyscrasias of the blood were not seriously considered in view of the short history and the physical signs.

Because of the severity of the abdominal signs, together with profuse bleeding by rectum, fever and leukocytosis, operation was advised. This was also concurred with by Dr. William Barclay Parsons, Jr., who saw the patient in consultation with us. Meanwhile, general preoperative supportive measures were instituted. A preoperative diagnosis of ileocecal intussusception was made.

Operation.—Under nitrogen monoxide-oxygen anesthesia, the peritoneal cavity was entered through a middle right rectus incision. No free fluid or evidence of peritonitis was noted. The intestinal coils were not distended. The appendix was normal in position and appearance, and the ileocecal region revealed no evidence of a recent intussusception. The whole extent of the colon was carefully examined, and nothing abnormal could be seen or felt. The ileum was then followed from the cecum proximally, and about 3 feet from the ileocecal junction a segment of slightly distended intestine was encountered, through the walls of which could be detected reddish-brown material, presumably blood. About midway along this blood-containing segment of intestine a Meckel's diverticulum was found arising from the antimesenteric border, at right angles to the long axis of the intestine. It was about from 10 to 12 cm. in length, the circumference equaling that of the adjacent ileum. It coursed downward, forward and mesad, and the tip continued as a very thin, pale, delicate threadlike process which was attached to the anterior abdominal wall a little below the umbilicus. The diverticulum was not distended, nor did it appear to be acutely inflamed. Along the proximal half of its inferior surface there was noted the attachment of a mesenteriolum containing a single large blood vessel. The intestines were then carefully examined up to the duodenojejunal junction, and nothing abnormal could be detected. The mesentery of the

diverticulum was ligated and divided, after which the base of the diverticulum was clamped, cut and cauterized with invagination of the stump in purse string fashion. A few reenforcing seromuscular Lembert sutures were then placed around the site of inversion. The caliber of the adjacent intestine did not seem to be appreciably diminished. The appendix was also removed.

Postoperative Course.—The patient had a moderate reaction following the operation, the pulse remaining somewhat rapid for the following three days and the temperature gradually subsiding until it became normal on the third day. There was no nausea, vomiting or distention, and subsequent rectal treatments and bowel movements revealed no more evidence of blood. There was moderate pain from the wound, but nothing simulating the severe colicky pain felt previous to the operation. The wound remained clean and healed. The patient was out of bed on the thirteenth day and was allowed to go home on the twenty-first. Before his discharge from the hospital, an enema of barium sulphate was given and a series of roentgenograms of the gastro-intestinal tract were made. The former showed no delay in filling the colon and cecum, and the whole large bowel appeared to be normal. After evacuation there were no shadows suggesting diverticula. The series of roentgenograms revealed a normal, freely movable, nontender, medium-sized stomach. There was no delayed emptying time, and the outline of the stomach was regular. Under the fluoroscope, the duodenal bulb seemed irritable, but the films revealed no deformity or evidence of an organic lesion. At six hours there was a small collection of barium in the terminal ileum, but the roentgenologist was not certain whether this was at the site of the previously removed diverticulum or at the ileocecal junction. At twenty-four hours nothing abnormal was seen. Since the patient's discharge he has been seen from time to time, and at a visit made recently, twenty-seven months after operation, he looked well. His color was good, and he showed moderate development in stature. He complained, however, of constipation and cramplike pains on the left side of the abdomen, which he had had for the past three months. He had no symptoms referable to the scar, the umbilical region or the right lower quadrant. His appetite was good, there were no digestive disturbances, and at no time since the operation had he noticed bloody or tarry stools. Examination revealed that the patient was in good physical condition. He was obviously apprehensive and worried for fear that there might be some new serious malady lurking in his abdomen. Inspection of the abdomen showed nothing abnormal. The scar was well healed and firm. Palpation disclosed nothing unusual except tenderness in the left lower quadrant over the sigmoid, which could be felt. There were no other masses or tender areas. Rectal examination gave negative results. Analysis of the stool showed no evidence of blood, ova or parasites. An enema of barium sulphate revealed a normal colon except for rather marked spasm of the descending colon with slight diminution in the depth and number of haustrations when compared with the findings two years before. A series of roentgenograms of the gastro-intestinal tract and a study of the ileum were also made, and they failed to show any evidence of a gastric, duodenal, jejunal or ileal pathologic process. In view of these findings, it was thought that the patient's symptoms might be due to a spastic colon. He was therefore placed on a semibland diet and given moderate doses of sodium nitrite and tincture of belladonna. The response to this regimen was good, and two months later he was entirely symptom-free, whereupon the antispasmodic therapy was discontinued, and he indulged in a liberal, well balanced diet without ill effect. He was last seen Dec. 16, 1932, three years after his operation. He had been feeling extremely well, had gained considerable weight and was moderately active in athletics. His habits are excellent, and his bowels move regularly.

There are no abdominal pains, and he has no symptoms referable to his scar or former illness. Examination showed him to be in splendid condition. The abdomen was soft, and the scar was firm; no masses were felt, and there were no areas of tenderness. The follow-up result has, therefore, been most satisfactory.

Pathologic Examination.—The diverticulum, which had shrunken considerably after fixation in a diluted solution of formaldehyde, measured about 4 cm. in length. The peritoneal coat was smooth, but at one point showed some small nodular projections about 1 mm. in diameter. The remains of the threadlike adhesion could be seen at the tip (fig. 1, *B*). The diverticulum was bisected longitudinally, and the lumen seemed empty. The knife decapitated an isolated pedunculated tumor which sprang from one lateral surface of the mucous membrane in the distal portion over an area 4 mm. in diameter. It was rounded and slightly nodular, and measured 7 mm. in length, 5 mm. in width and 4 mm. in height. The mucous membrane of the diverticulum seemed to be pink and intact, and had many papillary elevations less than 1 mm. in diameter, which represented appar-

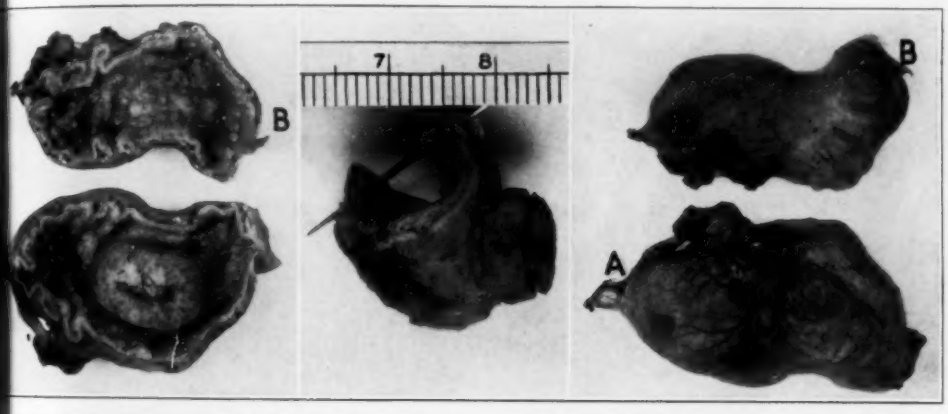

Fig. 1.—Photograph of a Meckel's diverticulum enlarged one and one-half times. At the right is shown the external surface with dilated subserosal vessels. *A* is the portion of the diverticulum which was attached to the ileum; *B*, the remnant of the adhesion at the tip. In the middle is shown the pedunculated adenomatous growth attached to the mucosal surface of the diverticulum. Its dome has been replaced after sectioning. Note the hyperplastic nodules of lymphoid tissue scattered over the mucosal surface of the diverticulum. At the left is shown a bird's eye view of the mucosal surface of the diverticulum after longitudinal section. The adenoma is shown in the lower half, bisected. The dark striations on the cut surface are engorged blood vessels.

ently hyperplastic lymphoid tissue. The tumor, on cross-section, appeared solid and pink and had numerous threadlike blood vessels radiating from the center toward the periphery. Sections taken through the wall of the diverticulum showed that it had the coats represented in the ileum, and that the glands were of the tubular mucous variety found there, shown in figures 2 and 5. The only changes from the normal that were recognized were the presence in the mucosa of an unusually large number of capillaries, somewhat dilated and congested. In the submucosa there were dilated, thin-walled veins and lymphatics. The former were widely distended with blood. Sections of the tumor showed that it was composed

of many tubular glands lined with cuboidal cells, among which could be recognized the chief and parietal cells which are typical of the glands of the stomach and a few characteristic Brunner's glands. The outer surface of the growth was covered with mucous glands. In the stalk or pedicle of the tumor there were dilated veins like those noted in the submucosa of the diverticulum. Further out in the tumor there were dilated capillaries filled with blood cells between almost every gland. A few red blood cells were found adherent to the surface of the growth. Figures 3 and 4 show the section under low and high power magnification, with Brunner's glands indicated at *A*. The growth, therefore, is a pedunculated adenoma composed of gastric and duodenal glands.

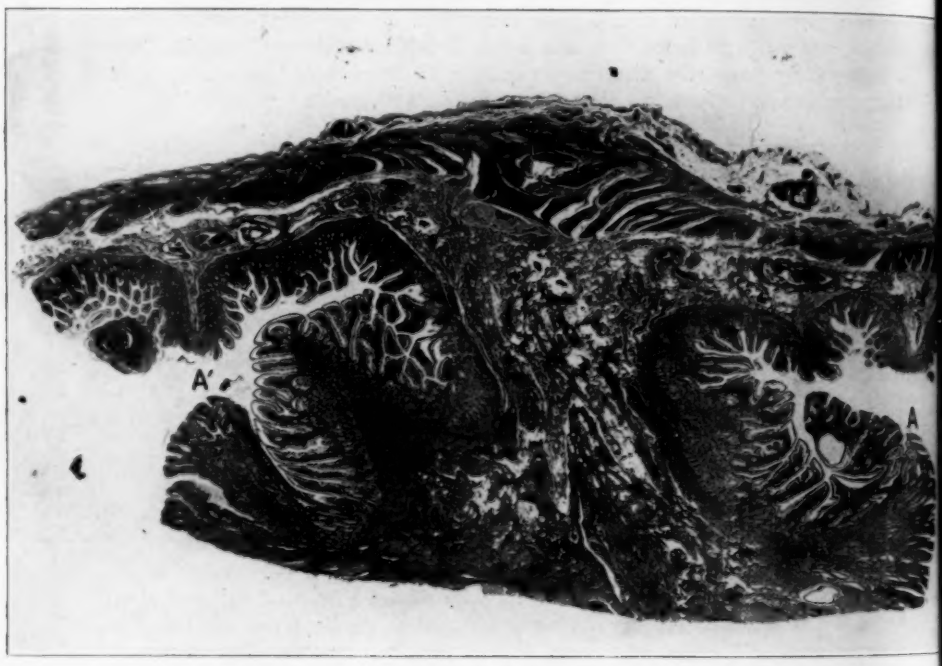

Fig. 2.—Low power photomicrograph of a longitudinal section through the wall of the diverticulum and the stalk of the adenoma. The stalk has a core of vascular submucosal fibrous tissue and is clothed as far as *A A'* with diverticulum mucosa. Beyond these points the adenoma proper begins.

A review of the literature has failed to reveal another example of gastric and duodenal gland adenoma of Meckel's diverticulum. In 1912, Lecène found an adenoma at the tip of a Meckel's diverticulum which lay in the submucosa and muscularis and was covered with intact mucosa, but this was composed of mucous glands resembling those of the intestine. Hertzler and Gibson found a small intramural mass at the apex of a Meckel's diverticulum composed of tubules resembling Brunner's glands. The superficial portion consisted of glandular tissue similar to pancreatic and intestinal glands. Bize also described a nodule

at the apex of a Meckel's diverticulum, situated in the submucosa and muscularis. It presented a picture of pancreatic glands, but certain portions of the nodule were the seat of glandular new growth arising from the ducts and having the characteristics of adenoma. "One may see the large ducts lined with cylindrical epithelium branching into a variable number of secondary ducts which are very short and terminate in the large cul-de-sacs of adenomatous tissue." He did not state whether the adenomatous portions of the tumor resembled gastric or

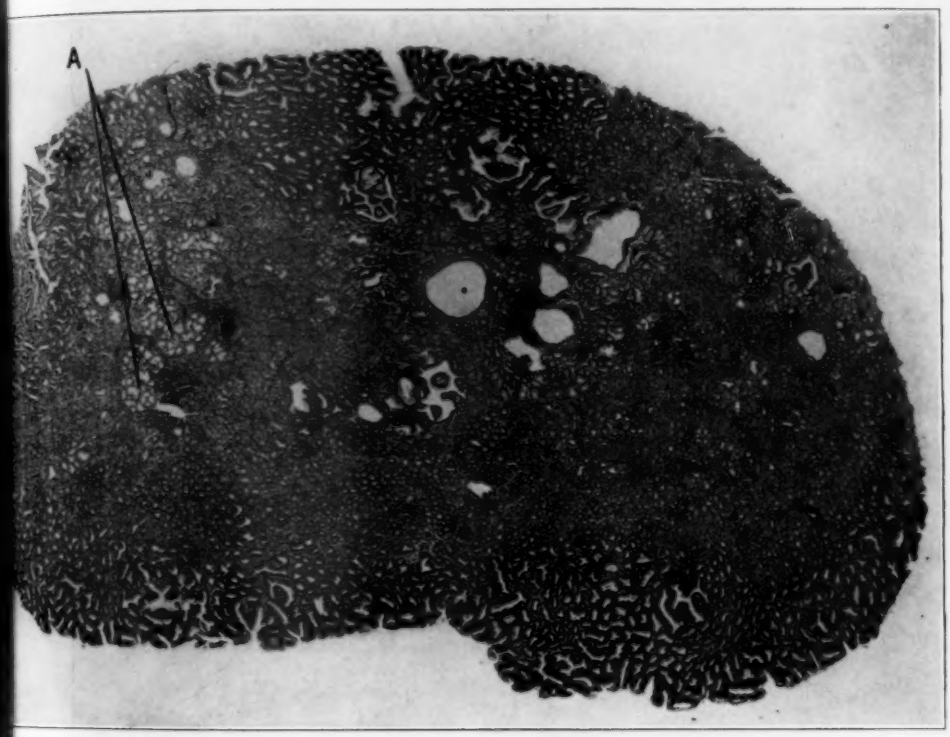

Fig. 3.—Low power photomicrograph of a cross-section through the adenoma taken at right angles to the axis of the pedicle. The entire periphery of the section is covered with a layer of mucous glands. Mucous glands also appear at intervals through the central portion, forming dilated cystic cavities lined with columnar goblet cells. The many tiny round acini forming the bulk of the central part of the section are simple gastric glands. At *A* are shown groups of Brunner's glands.

intestinal glands. Other neoplasms which have been reported include polyps, lipomas, myomas, angiomas, myxomas, sarcomas, carcinomas and carcinoids, but none of these has had gastric or duodenal elements in them. There is no occasion for surprise that an adenoma of the

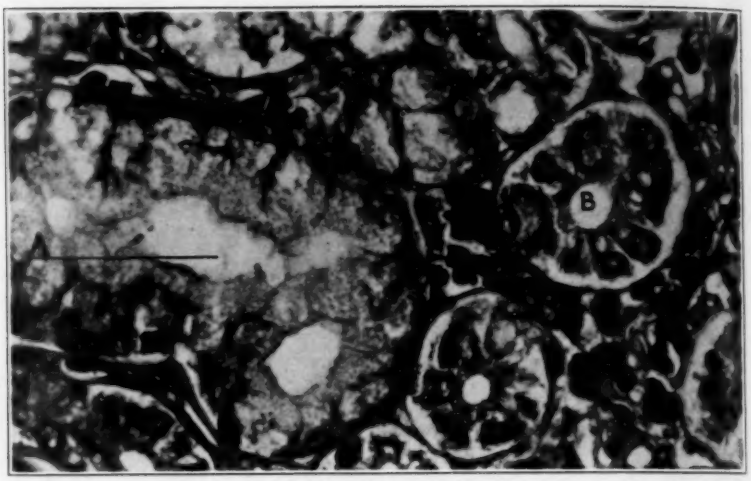

Fig. 4.—High power photomicrograph of the adenoma showing at *A* one of Brunner's glands and at *B* a simple gastric gland. The acinus is lined with chief cells and at the left is a parietal cell with larger granules in the cytoplasm.

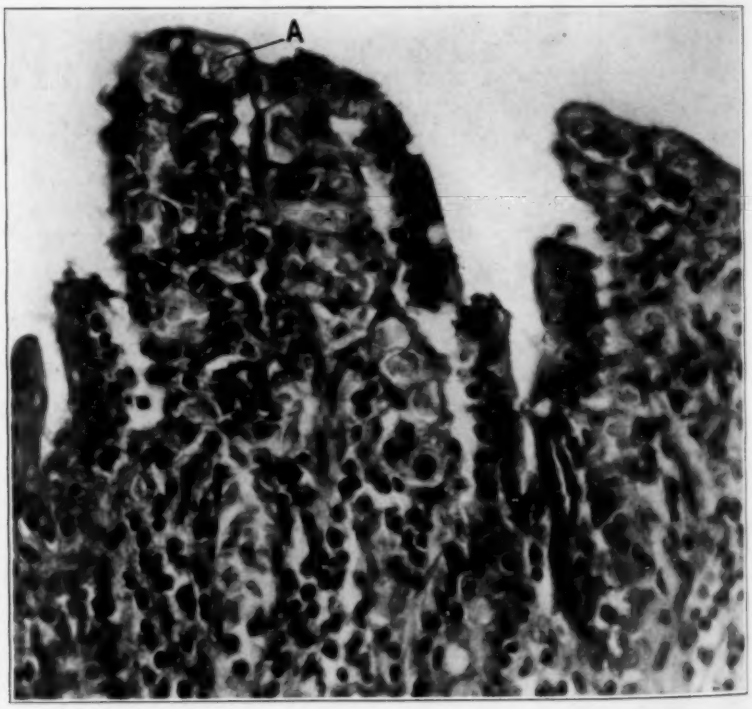

Fig. 5.—High power photomicrograph showing a fold of the mucosa of the diverticulum containing an unusually large number of capillaries. In some places, as at *A*, these are separated from the lumen only by the thinnest of membranes.

gastric type should be found in this situation, because heterotopic gastric and pancreatic tissue has frequently been noted in the diverticulum, and adenomatous growths composed of these tissues have been found in other parts of the alimentary tract. In connection with external fistulas of the umbilicus, adenomas have been described which usually are covered with mucosa of the intestinal type but sometimes are covered, in whole or in part, with gastric mucosa, and even may have gastric gland adenomas within their central portion. It is our belief (and the belief of others) that Meckel's diverticulum and these umbilical fistulas and polyps are persisting remnants of the vitelline (omphalomesenteric) duct. We have wondered why these structures have sometimes contained apparently heterotopic tissue, and in searching for an adequate hypothesis we have been compelled to review the whole question of alimentary heterotopia. We propose to discuss this question in a subsequent paper.

CLINICAL FEATURES

Bleeding from Peptic Ulcer of Meckel's Diverticulum.—The outstanding clinical feature of the present case, namely bleeding, merits some discussion, because bleeding from a Meckel's diverticulum is usually associated with an ulcer of that embryonic remnant. This has been emphasized by numerous observers, and more recently the recorded cases have been reviewed and summarized by Aschner and Karelitz, Lindau and Wulff and Greenwald and Steiner, the last named investigators, however, having included other lesions of Meckel's diverticulum as well. By combining the tabulations of these three groups of observers with subsequent case reports, we have been able to list sixty-eight cases.[2] They have been placed in two main groups, namely, the group

2. We do not think that cases 8, 19, 32 and 37 in Lindau and Wulff's list should be accepted. Cases 8 and 37 are self-explanatory on consulting their table. Case 19 (Taylor) was not found after careful study of his paper. Case 32 was not accepted because the pathologic process was found in a large congenital diverticulum, whereas Meckel's diverticulum, which was also present, revealed no pathologic process. We were unable to obtain the references for cases 20 and 21, but we accepted these. Zimmermann's case is doubtful, because in his description an acute inflammatory process of the whole diverticulum is indicated, and it is possible that the ulcer might have resulted from this rather than from the more chronic localized lesion with which we are wont to associate peptic ulcer. For the same reason Hudson and Koplik's three cases are probably doubtful, and they state this in their paper. Winkelbauer's seventh case is also questionable as the bleeding may have occurred from the intussusception. Hess and Rosenblum's case is the same as case 2 of Abt and Strauss. Recently Borrmann reported a case of a large Meckel's diverticulum, 66 cm. long, in a boy of 14 who died of intestinal hemorrhage. At autopsy, an ulcer was found in the intestine close to, but not at the opening of, the diverticulum. We therefore did not include this case.

TABLE 1.—*Peptic Ulcer of Meckel's Diverticulum, Mucosa Investigated*

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Denecke.....	1902	7	M	Absent	Perforation at base of diverticulum; no gastric mucosa found	Died (operation, autopsy)
Hilgenreiner...	1903	18	M	Present	Ulcer near tip of diverticulum at margin of intestinal mucosa; gastric mucosa present ?	Recovery
Deetz.....	1907	9	M	Absent	Perforated ulcer at base; gastric mucosa and pancreatic tissue	Recovery
Hübschmann..	1913	4½	M	Present	Perforated ulcer at base at margin of gastric mucosa	Died (operation, autopsy)
Gramen.....	1915	10	M	Not stated	Perforated ulcer at base at margin of gastric mucosa	Recovery
Callender.....	1915	19 mo.	Not stated	Present	Ulcer at border of diverticulum and ileum; eroded vessel at margin; gastric mucosa	Died (autopsy, no operation)
Meulengracht..	1918	12	M	Present	Penetrating ulcer near tip in intestinal mucosa; gastric mucosa close by inside pocket	Died (autopsy, no operation)
Müller.....	1919	11	M	Present	Perforated ulcer at midportion in intestinal mucosa; gastric mucosa also present	Recovery
Mégevaud and Dunant	1922	28	M	Present	Ulcer at base at border of gastric mucosa; eroded artery	Recovery
Brasser.....	1924	15	M	Present	Perforated marginal ulcer; gastric mucosa	Died (operation, autopsy)
Humbert.....	1924	11 mo.	M	Present	Perforated ulcer near apex, adjacent to gastric mucosa	Died (operation, autopsy)
Guibal.....	1924	14	M	Present	Penetrating ulcer near base adjacent to gastric mucosa; three eroded arteries	Recovery
Pascale.....	1925	41	F	Present	Perforating ulcer in midportion; gastric mucosa present	Recovery
Ulrich.....	1925	8 mo.	M	Present	Perforated ulcer in intestinal mucosa; gastric mucosa present	Died (operation, autopsy)
Abt and Strauss Case 1	1926	20 mo.	F	Present	Ulcer near apex; gastric mucosa at apex	Recovery
Etchegorry....	1926	16	M	Present	Perforated ulcer between gastric and normal mucosa	Recovery
Kleinschmidt... Case 1	1927	15	M	Present	Perforated ulcer near base; gastric mucosa	Recovery
Jackson, A. S..	1927	14	M	Present	Ulcer at border of gastric mucosa; correct preoperative diagnosis	Recovery
McCalla.....	1927	4	M	Present	Perforated ulcer at base; gastric mucosa	Died (autopsy, no operation)
Büchner.....	1927	24	M	Not stated	Ulcer at base between gastric and intestinal mucosa	Died
Gramen.....	1927	11	F	Not stated	Peptic ulcer; gastric mucosa ?	Recovery
Gramen.....	1927	21	M	Not stated	Peptic ulcer; gastric mucosa ?	Recovery
Meiss.....	1928	2	M	Present	Ulcer near tip at border of gastric mucosa	Recovery
Hartglass.....	1928	4	F	Absent	Perforated ulcer at base at margin of gastric mucosa	Recovery
Peterman and Seeger	1928	6	M	Present	Penetrating ulcer at base; gastric mucosa; correct preoperative diagnosis	Recovery

TABLE 1.—*Peptic Ulcer of Meckel's Diverticulum, Mucosa Investigated—Continued*

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Franke.....	1929	Not stated		Not stated	Ulcer in intestinal mucosa; gastric mucosa at tip	Died
Winkelbauer... Case 6	1929	2	M	Present	Ulcer at base in normal mucosa; gastric mucosa close by	Recovery
Treplin.....	1929	Not stated		Not stated	Ulcer in normal mucosa; gastric mucosa	Recovery
Winkelbauer... Case 7	1929	19 mo.	M	Present	Ulcer with eroded vessel; no heterotopia; invagination of diverticulum with intussusception as well	Recovery
Aschner and Karelitz Case 1	1930	15 mo.	F	Present	Penetrating ulcer at base at margin of gastric mucosa	Recovery
Aschner and Karelitz Case 2	1930	26 mo.	M	Present	Ulcer at base adjacent to gastric mucosa	Recovery
von Haberer... Case 1	1930	13	M	Present	Ulcer near tip adjacent to gastric mucosa	Recovery
von Haberer... Case 2	1930	21	M	Present	Ulcer at base adjacent to gastric mucosa	Recovery
Schmidt.....	1930	18	M	Not stated	Two ulcers at border of gastric mucosa; one had perforated	Recovery
Fevré, Patel and Lepart Case 1	1930	7	M	Absent	Perforated ulcer at base at border of duodenal mucosa which lined the diverticulum	Recovery
Fevré, Patel and Lepart Case 2	1930	5 mo.	M	Present	Perforated ulcer at base at border of gastric mucosa	Recovery
Green..... Case 4	1930	6½ mo.	M	Present	Large diverticulum 40½ inches long with dilated bulbous end, separated from rest of diverticulum by a constriction; perforated ulcer in tip; 3 ulcers found 12 inches from distal extremity; tip lined with pyloric mucosa; gastric mucosa also found at site of other ulcers; elsewhere diverticulum lined with intestinal mucosa	Died (operation, no autopsy)
Büchner.....	1931	8	F	Not stated	Ulcer at border of gastric mucosa	Recovery
Lindau and Wulff Case 1	1931	15	M	Absent	Perforated ulcer near tip in normal mucosa; polyp contained gastric mucosa	Died (operation, autopsy)
Greenwald and Steiner Case 1	1931	15 wk.	M	Present	Perforated ulcer at base; gastric mucosa; correct preoperative diagnosis	Died (operation, no autopsy)
Greenwald and Steiner Case 2	1931	10	M	Absent	Perforated ulcer at base; gastric mucosa	Recovery
Cobb.....	1931	18	M	Present	Perforation near base at border of gastric mucosa	Recovery
Debré, Bopp and Semelaigne	1931	17 mo.	M	Present	Ulcer at base which had perforated into transverse colon; inflammatory reaction immediately around it, but no general peritonitis; diverticulum lined with gastric mucosa	Died (operation, no autopsy)
de Vernejoiel...	1932	5	M	Present	Perforation at base with surrounding zone of induration; ulcer at border between gastric and intestinal mucosa	Recovery
Hudson and Koplik Case 13	1932	6	M	Present	Perforation of diverticulum, with peritonitis; ulcer at junction of gastric and intestinal mucosa	Died (operation, no autopsy)

TABLE 1.—*Peptic Ulcer of Meckel's Diverticulum, Mucosa Investigated—Continued*

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Hudson and Koplik Case 25	1932	5	F	Present	Perforation at base, with peritonitis; ulcer in intestinal mucosa at junction with gastric mucosa; resection of diverticulum	Recovery
Hudson and Koplik Case 31	1932	5	M	Present	Sigmoid distended with blood; ulcer found on microscopic examination; gastric and intestinal mucosa	Recovery
Mason and Graham	1932	9 mo.	M	Present	Excision of diverticulum; most of it lined with gastric mucosa; pancreatic tissue at tip; ulcer at border between gastric and intestinal mucosa, but involving the gastric mucosa	Recovery
McKeen.....	1932	53	M	Present	Ulcer near tip which had perforated and was adherent to ascending colon and surrounded with adhesions; diverticulum lined with intestinal mucosa	Recovery
Schaaf.....	1932	7	M	Present	Bloody peritoneal exudate; intramesenteric diverticulum 60 cm. long running parallel to ileum; perforation of diverticulum about midway close to mesenteric attachment of ileum; gastric mucosa lined distal two thirds of diverticulum; ulcer in gastric mucosa at site of perforation; correct preoperative diagnosis	Recovery
Vaughan and Singer	1932	7	M	Absent	Perforated ulcer near tip between gastric and intestinal mucosa, located in intestinal side	Recovery
Roudil and Marty	1932	7	F	Absent	Perforated ulcer at tip; necrosis of mucosa at distal end; author states necrotic mucosa impresses him as gastric	Died (operation, no autopsy)
Total = 52 cases						

in which the mucosa was examined microscopically (table 1) and the group in which microscopic examination of the mucosa was lacking (table 2). There was no designation of sex in four cases; only ten of the patients were females, and the rest, fifty-four, or 85 per cent, were males. The average age of sixty-six patients (ages not stated for two) was 10.4 years; forty-two were 10 years or under (63 per cent) and fourteen were between 11 and 20 years of age (21 per cent), so that a total of fifty-six, or 84.5 per cent, of the patients were in the first two decades of life. The oldest patient was 53. Twenty-one died, making a mortality of 30 per cent. In thirty-five the ulcer had perforated, resulting in diffuse or spreading peritonitis, so that it is not surprising to learn that fifteen of these patients died. In other words, of twenty-one patients in the group with ulcer who died, fifteen died as a result of perforation of the ulcer. Bleeding was present in fifty-one, or 75 per cent, of those with ulcer (absent in seven and not mentioned for ten). In all but seven of the cases listed in table

1, gastric mucosa was microscopically identified. One of the seven excepted diverticula contained duodenal mucosa (Fevré, Patel and Lepart's first case); three others revealed normal intestinal mucosa (Winkelbauer, case 7, McKeen, and Denecke), and in three the character of the mucosa was doubtful (Gramen, two cases; Roudil and Marty, one case). A correct preoperative diagnosis of ulcer of Meckel's diverticulum was made in only six instances, namely, in A. S. Jackson's case, by the family physician, Dr. Ketterer (who also attended R. H. Jackson's patient of several years previously); in the case of Peterman and Seeger; in case 2 of Shanon; in the case of Schwarz and Daly; in case 1 of Greenwald and Steiner, and in the case of Schaaf. Aschner and Karelitz's first case, Coleman's third case and Brennecke's fifth case were all diagnosed as "Meckel's diverticulum," while Wolfson and Clurman correctly diagnosed a case of acute Meckel's diverticulitis. Lately Hudson and Koplik made a correct preoperative diagnosis twice (cases 29 and 32), and Faust did likewise in his second case. The fact that almost four times as many cases of ulcer of Meckel's diverticulum have been reported in the six years following Stulz and Worringer's collection of fourteen cases in 1926 makes it evident that this condition is being more widely appreciated and physicians will therefore be better able to recognize it preoperatively in subsequent cases.

The ulcer usually resembles in structure the peptic ulcer of the stomach or of the duodenum. It is often situated at the border between the two types of mucosa and consequently near the base of the diverticulum. In a certain number of these marginal or border ulcers the lesion will be found in the end-zone of the normal mucosa, but the edge of the ulcer will extend to the line of division between the normal and the heterotopic mucosa. Sometimes the ulcer is found completely in the intestinal mucosa of the diverticulum, a short distance from the heterotopic area. In still other instances the ulcer is located entirely within the aberrant tissue, and therefore this type of ulcer may be found at or near the tip of the diverticulum.

The bleeding in this group, when it occurs, appears usually as blood *unmixed* with mucus in the stools. This, together with the absence of a palpable mass, is considered a rather important differential point in distinguishing this condition from intussusception. In addition, the bloody stools are apt to be more frequent and greater in amount, whereas in intussusception one may obtain a history of only two or three small movements disclosing blood *mixed* with mucus or just some blood-stained mucus on the examining glove. Some of the patients in this group gave an account of repeated hemorrhages, preceded sometimes by slight constipation and associated with vague generalized

abdominal or periumbilical pains. Such episodes might occur over a relatively long or short period of time with intervals of months or years between them. The signs may therefore vary considerably, but the histories in many of the cases indicated that the patients were moderately, if not acutely, ill, that they were sometimes strikingly anemic, and that when the hemorrhage was profuse or if perforation of the ulcer had taken place, they exhibited a certain degree of shock.

TABLE 2.—*Peptic Ulcer of Meckel's Diverticulum, Mucosa not Investigated*

Author	Year	Age, Years	Sex	Hemorrhage by Rectum	Comments	Result
Brentano.....	1904	21	M	Not stated	Perforated ulcer	Recovery
Läwen.....	1909	23	M	Not stated	Perforated ulcer near base; eroded artery	Recovery
Griffith.....	1914	19 mo.	M	Present	Perforated ulcer at tip; peridiverticular abscess	Died (autopsy, no operation)
Jackson, R. H.	1924	10	M	Present	Ulcer at base; eroded artery	Recovery
Schreuder.....	1925	8	M	Present	Pancreatic tissue at tip; ulcer at base; eroded artery; patient also had a duodenal ulcer	Recovery
Stulz and Woringer Case 1	1926	4	M	Present	Perforated ulcer at base	Died (operation, no autopsy)
Stulz and Woringer Case 2	1926	11 mo.	M	Present	Perforated ulcer at base, with abscess at site of perforation	Died (autopsy, no operation)
Abt and Strauss Case 2	1926	11 mo.	M	Present	Ulcers at tip	Recovery
Moore..... Case 2	1926	9 mo.	M	Present	Ulcer at base	Recovery
Moll.....	1926	5 mo.	Not stated	Present	Two ulcers at base of large diverticulum, 33½ inches long	Died (operation, autopsy)
Fuss.....	1927	37	F	Present	Bleeding ulcer near fundus, extending to muscular coat	Recovery
Kleinschmidt... Case 2	1927	45	M	Present	Perforated ulcer	Recovery
Shanon..... Case 2	1928	18 mo.	F	Present	Perforating ulcer with attachment to bladder; correct preoperative diagnosis	Recovery
Smith and Hill	1929	14 mo.	M	Present	Perforated ulcer at tip	Recovery
Schwarz and Daly	1929	8	M	Present	Ulcer with large eroded artery at base; correct preoperative diagnosis	Recovery
Walters and Wilkins	1932	20	M	Present	Perforated ulcer near base	Died (operation, autopsy)
Total = 16 cases						

In those cases in which signs of an acute abdominal lesion are lacking, the situation is often misleading, and Gray made the pertinent observation that acute lesions of Meckel's diverticulum may transform a picture of relatively good condition and well-being into one of sudden acute illness with signs of peritonitis and even shock. At operation, one may find perforation of the ulcer or evidence of severe hemorrhage into the adjacent intestinal coils. In a recent article, Vaughan and Singer also stated that the onset of symptoms may be gradual or

sudden. They emphasized the fact that sudden severe pain in the lower part of the abdomen, especially in children, associated with rigidity, leukocytosis and signs of beginning collapse or shock should lead one to suspect a perforated Meckel's diverticulum. They pointed out that in acute appendicitis, as a rule, the signs of acute diffuse peritonitis from perforation are apt to develop only after several hours, perhaps a day, following the initial symptoms. The tendency to spontaneous sealing of the perforation of a Meckel's diverticulum is also mentioned by them.

In the discussion of ulcer of Meckel's diverticulum, Fevré, Patel and Lepart emphasized the following points: 1. A young man with a history of recent hemorrhages by rectum followed by a picture of acute peritonitis (at which time the surgeon is usually called) must always make one suspicious of a perforated ulcer of Meckel's diverticulum. 2. With a history of bleeding of unknown origin, one must never close an abdomen without searching for Meckel's diverticulum. 3. If one operates for intestinal hemorrhage and Meckel's diverticulum is found, it should be removed regardless of its outwardly harmless and grossly normal appearance (this was certainly true in our case). 4. In any case of gastro-intestinal bleeding in infants or boys, when the cause is not determined, celiotomy should be performed before the signs of acute disaster develop. 5. It is important to search for a Meckel's diverticulum as the possible cause of peritonitis of undetermined origin. 6. Finally, it is important to seek a Meckel's diverticulum when the operative findings are not in accord with the preoperative diagnosis.

Mondor even goes so far as to state that in a proved case of acute appendicitis, if there has been a previous history of intestinal bleeding of undetermined source, one should examine the ileum for a Meckel's diverticulum, and if it is found, the diverticulum as well as the appendix should be removed. We are not in agreement with this statement because of the danger of spreading an otherwise localized peritonitis.

Bleeding from Causes Other Than Ulcer or Invagination of Meckel's Diverticulum.—We have found a number of instances in the literature (table 3) in which bleeding from a Meckel's diverticulum developed in connection with lesions not associated with ulcer or invagination, and yet it frequently appeared as the presenting symptom. This is certainly true of the case we report in this paper. There was no ulcer in the diverticulum, and the lining mucosa seemed to be intact. Even the surface of the adenoma revealed no break in continuity. The cases of Webster, Mayo and Johnson, Abt and Strauss (case 3) and Brennecke (case 5) presumably showed no interruption of the normal lining mucosa. Of still greater interest to us are those diverticula listed in table 3 which revealed heterotopic tissue without macroscopic interruption of the mucosal continuity, in spite of the clinical occurrence

TABLE 3.—*Meckel's Diverticulum with Bleeding from Causes Other Than Peptic Ulcer or Invagination*

Author	Year	Age, Years	Sex	Comments	Result
Webster	1902	42	F	Bloody stool once; diverticulum in left inguinal hernia	Recovery
Brennecke. Case 5	1913	25	M	Recurrent bleeding by rectum; diverticulum filled with blood; mucosa thick, pale, redundant, firm; no ulcer noted; no acute inflammation; no microscopic report; preoperative diagnosis of "Meckel's diverticulum"	Recovery
Stern. Case 16	1917	3	M	Repeated bloody stools; perforation of diverticulum with ulcerative phlegmonous process of the whole diverticular wall; diffuse peritonitis	Died
Mayo and Johnson	1926	15	M	Repeated bleeding by rectum; ileum thickened above and below diverticulum, which was swollen and edematous	Recovery
Stone, J. B.	1926	14 mo.	Not stated	Bleeding; pancreatic tissue in wall of diverticulum; mucosa that of ileum	Died
Abt and Strauss. Case 3	1926	11 mo.	M	Repeated hemorrhage by rectum; large diverticulum, 18 inches long, in mesentery of intestine; no heterotopia or ulcer found	Recovery
Rowan. Case 2	1926	Not stated	M	Attacks of bleeding by rectum; at second operation diverticulum was found with perforation and a papilloma; cause of perforation not stated	Recovery
Tisdall	1928	11 mo.	M	Marked anemia; bloody stools; died of bronchopneumonia; large diverticulum in mesentery; gastric mucosa found but no ulcer	Died
Härting	1928	64	F	Bleeding by rectum; myoma of diverticulum found	Recovery
Harrington	1929	67	M	Mass of intestinal coils matted down between bladder and rectum; in midst of these coils inflamed diverticulum was found with perforations into several loops of intestine, bladder and rectosigmoid	Recovery
Faust and Walters	1931	62	M	Recurrent bleeding by rectum; fibrosarcoma at tip of diverticulum measuring 9 by 7 by 5 cm. and adherent to dome of bladder	Recovery
Hudson and Koplik. Case 2	1932	1½	M	Bleeding diverticulum with hemorrhage into lumen of adjacent intestine; no pathologic report	Recovery
Hudson and Koplik. Case 15	1932	2 mo.	M	Blood on rectal examination; obstruction from fibrous cord running from tip of diverticulum to mesentery of ileum; release of obstruction; resection of diverticulum	Recovery
Hudson and Koplik. Case 16	1932	10	F	Bloody diarrhea; blood in intestine and diverticulum; latter showed gastric mucosa, which appeared intact; capillary extravasation in mucosa; no ulcer	Recovery
Hudson and Koplik. Case 17	1932	6	M	Bloody "tissue" in stools; obstruction from diverticulum adherent to mesentery overlying and constricting ileum; resection	Recovery
Hudson and Koplik. Case 18	1932	13 mo.	F	Profuse hemorrhage by rectum; diverticulum found; not resected	Recovery (improved)
Hudson and Koplik. Case 20	1932	1¼	F	Profuse hemorrhage by rectum; gastric and intestinal mucosa in diverticulum; resection; no mention of ulcer; considerable recent hemorrhage in all layers	Recovery
Hudson and Koplik. Case 29	1932	9½	F	Old and fresh blood in stools; tip of diverticulum adherent to mesentery; ileum matted together about diverticulum by adhesions; gastric mucosa; resection; no ulcer; enterostomy; correct preoperative diagnosis	Recovery

TABLE 3.—*Meckel's Diverticulum with Bleeding from Causes Other Than Peptic Ulcer or Invagination—Continued*

Author	Year	Age, Years	Sex	Comments	Result
Hudson and Koplik.... Case 32	1932	5½	F	Bleeding by rectum; acutely inflamed diverticulum; gastric mucosa; no ulceration; correct preoperative diagnosis	Recovery
Faust..... Case 1	1932	67	M	Previous attack of pain in lower part of abdomen associated with diarrhea and several passages of dark blood; distended diverticulum with narrow neck; perforation into bladder and sigmoid wall; abscess walled off by surrounding loops of ileum	Recovery
Faust..... Case 2	1932	61	M	Several episodes of profuse hemorrhage by rectum; then signs of ileus; diverticulum composed of inflammatory mass obstructing one of ileal loops; many adhesions from adjacent coils; correct preoperative diagnosis	Recovery
Stout and Schullinger	1933	16	M	Profuse hemorrhage; adenoma of diverticulum composed of gastric and duodenal glands; no ulcer found; mucosa intact	Recovery

of bleeding, because they seem to lend support to our observations as to the source of the bleeding in our own case (J. B. Stone, Tisdall, Hudson and Koplik, cases 16, 20, 29 and 32). The case reports of Härting, J. B. Stone, and Faust and Walters indicate that certain tumors may be the source of bleeding from Meckel's diverticulum.[3] In the remaining cases listed in table 3 there was also exhibited bleeding from pathologic conditions of the diverticulum other than ulcer or invagination. Here again, in this group, the associated symptoms fail to disclose any similarity with the exception, perhaps, of abdominal pain. It appears, then, from the study of table 3, that bleeding can and does take place in processes other than ulcer or invagination of this embryonic remnant, and that it can occur apparently even in the presence of grossly intact normal and heterotopic mucosa. This has recently been emphasized by Hudson and Koplik.

Bleeding from Invagination With or Without an Associated Intussusception.—A few cases (table 4) have been chosen simply to illustrate that bleeding may also take place in connection with invagination of the diverticulum into the intestine with or without an associated intestinal intussusception. When bleeding results from invagination of the diverticulum alone, without any intussusception of the intestine proper, the bleeding may be attributed to the diverticulum, especially to the mucosa at the base of the diverticulum.

3. We did not include in table 3 Michaels' recently reported case of tuberculous ulcer of Meckel's diverticulum, because the bleeding may have originated from the tuberculous process involving the ileocecal region and the hepatic flexure.

We hesitate, therefore, to consider the group of cases of ulcer (tables 1 and 2) as a distinct clinical entity because our own patient, displaying most of the signs of bleeding ulcer of Meckel's diverticulum, failed to disclose any ulcer; the lesion was an adenoma instead. That there have been other instances in which the conditions simulated ulcer with bleeding is clearly shown in tables 3 and 4. We believe, then, that whereas ulcer is probably the commonest cause of bleeding from Meckel's diverticulum, there are other pathologic processes of that embryonic remnant which may produce a similar picture.

Other Clinical Symptoms and Signs in Connection with Lesions of Meckel's Diverticulum.—In addition to the occurrence of bleeding, a history of a slowly healing umbilicus or a persistent sinus at the umbilical region for a varying time after birth may also have some significance. Varying periods of constipation associated with vague, indefinite general abdominal or periumbilical pains are described in some of these cases. It has also been pointed out that persons with Meckel's diverticulum are apt to disclose other anomalies, such as harelip, cleft palate, dextrocardia, patent interventricular septum, meningocele, exstrophy of the bladder and incompletely rotated cecum. Christie found at autopsy congenital anomalies in one third of his sixty-three cases of Meckel's diverticulum. Symptoms may develop in the first months of postnatal life, more often in childhood, and even in the later periods of life, but in the great majority of cases symptoms are produced in the first two decades.

General Aspects of Meckel's Diverticulum.—The diverticulum may remain latent and symptomless throughout life. It has been found at from 2 to 3 per cent of all autopsies, and is about four times as common in males as in females, although ratios have been given as low as 2:1 and as high as 6:1. Of the sixty-eight diverticula showing peptic ulcers, all but nine certain and four questionable ones were found in males.

It is rare to find two or more cases of Meckel's diverticulum in the same family. It has been stated that in the group with ulcer, at least, the pain is not so sudden or so severe as in acute appendicitis, nor is the vomiting so constant or so persistent. Gray pointed out that acute Meckel's diverticulitis often starts during a period of body activity and exertion, while acute appendicitis frequently begins at night with the body at rest. Its position among the coils of the intestines probably renders it more dangerous than acute appendicitis, in which the process ordinarily seems to become localized more readily. The white blood cell count is often elevated, with a rise in the number of polymorphonuclear cells. The abdomen may be soft, but it is usually splinted in the umbilical and ileocecal regions. One may sometimes appreciate a palpable mass, but

not usually, unless there is an associated intussusception or an inflammatory mass with abscess formation. In determining the presence of a mass or a collection of exudate the rectal examination may furnish some information. Finally, one should note any abnormality of the umbilical cicatrix and the presence of meteorism around the region of the umbilicus, as well as any evidence of the anomalies previously mentioned.

With the passage of time, clinicians, especially pediatricians and surgeons, will become more impressed with the fact that a Meckel's diverticulum may be a cause of obscure abdominal symptoms, particularly in connection with bleeding, and even of acute abdominal conditions of undetermined origin, and therefore its existence will be discovered in the course of exploratory celiotomies more frequently. An illustration of this point is brought out by Baker, who, in 1930, found four cases of Meckel's diverticulum in the course of 150 laparotomies performed in a period of three months. Contrast this with McGlannan's observation, in 1922, that Meckel's diverticulum had been noted only three times in about 1,400 abdominal operations.

The general pathology of Meckel's diverticulum and its embryology have been thoroughly set forth by such authors as Fitz, Halstead, Eisendrath, Gray, Cheyne, Keith, Hilgenreiner, Cullen, Tillman, Waegeler, and Kelly and Hurden, and the reader who may be interested in these phases of the subject will find appropriate bibliographies at the close of the present paper.

In general, operative intervention is usually indicated because of the frequent existence of an acute abdominal condition. When the patient is very sick, it is better to temporize an hour or two in an effort to institute certain preoperative supportive measures. The operative procedure naturally depends on the lesion that is found. It would seem to be wiser to remove the diverticulum, provided one is not pressed for time and provided that its removal will not produce too much damage to the surrounding viscera and possibly favor a spread of infection if this is present. The mortality in the patients with acute inflammatory lesions was 40 per cent. In the patients in whom intussusception was caused by the diverticulum, the mortality was 60 per cent according to Gray and 68 per cent according to Halstead. In infants under 1 year of age in whom the diverticulum became acutely inflamed and was removed, the mortality was 100 per cent. The mortality in the group with ulcer was 30 per cent.

SUMMARY

We have reported an apparently unique case of Meckel's diverticulum in which the mucosal surface near the tip was the site of a nonulcerated pedunculated adenoma composed of gastric and duodenal glands.

TABLE 4.—*Some Cases of Bleeding from Invagination of Meckel's Diverticulum With or Without an Associated Intussusception*

Author	Year	Age, Years	Sex	Comments	Result
Weill and Frankel.....	1896	4½	F	Bloody stools; diffuse colon bacillus peritonitis; invagination of diverticulum with an ileal intussusception; reduction; resection of intussusception and diverticulum	Died
von Steubenrauch.....	1898	5½	F	Bleeding by rectum; invagination of diverticulum with intussusception of terminal ileum	Died
Brunner..... Case 3	1899	4	M	Blood in stools; abdominal pain; vomiting; accessory pancreas at tip of invaginated diverticulum; ileocecal intussusception; resection	Recovery
Robinson.....	1899	5	M	Abdominal pain; distention; a little blood in enema; enteric intussusception 4 inches long, with invaginated diverticulum; intussusception reduced, diverticulum excised	Died
Erdmann..... Case 2	1900	9	M	Blood in stool; ileal intussusception with invaginated diverticulum at apex; resection	Died
Morrison.....	1901	5	M	Bleeding by rectum; invagination of diverticulum with ileal intussusception; excision of diverticulum	Recovery
Wainwright.....	1902	17	M	Bleeding by rectum; invagination of diverticulum with intussusception of ileum; reduction; excision of diverticulum	Recovery
Dobson.....	1903	4½	M	Pain; vomiting; blood and mucus by rectum; ileocecal intussusception with invaginated diverticulum at apex; resection	Recovery
Terry.....	1903	12	M	Blood in stool; ileal intussusception with invaginated diverticulum at apex; reduction; excision of diverticulum	Recovery
Zum Busch.....	1903	21	M	Bloody stools; invaginated diverticulum at apex of ileocecal intussusception; subserous lipoma at tip of the diverticulum; resection	Recovery
Bousquet.....	1904	30	M	History of attacks of abdominal pain and blood in stool; palpable mass in right lower quadrant in last three attacks; ileocecal intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Bize.....	1904	6	F	Bleeding by rectum; pancreatic tissue at tip of diverticulum which was invaginated and produced an ileocecal intussusception; reduction; resection of diverticulum and adjacent loop of intestine	Died
Richter..... Case 2	1906	3	M	Abdominal pain; bloody mucus by rectum later; ileocecal intussusception with diverticulum at apex; reduction; excision of diverticulum	Died
Coffey.....	1907	7	M	History of blood by rectum; ileocolic intussusception with invaginated diverticulum at hepatic flexure; resection	Recovery
Bidwell.....	1907	3½	M	Bleeding by rectum; intussusception-reduction; recurrence of symptoms; invaginated diverticulum at apex of ileal intussusception; resection	Recovery
Kothe..... Case 1	1908	23	M	History of abdominal pain, vomiting, no bowel movement; bloody stool following rectal examination after induction of spinal anesthesia; ileocecal intussusception with diverticulum at apex; resection; Murphy button	Recovery

TABLE 4.—*Some Cases of Bleeding from Invagination of Meckel's Diverticulum With or Without an Associated Intussusception—Continued*

Author	Year	Age, Years	Sex	Comments	Result
Kothe..... Case 2	1908	7 mo.	M	Vomiting; distention; blood in enema return; small accessory pancreas at tip of invaginated diverticulum which formed the apex of an ileocolic intussusception; resection	Died
Gray.....	1908	8	M	Blood in stool; invaginated diverticulum at apex of ileocecal intussusception; partial reduction; resection	Died
Drummond..... Case 1	1912	5	M	Abdominal pain; bleeding by rectum; ileal intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Drummond..... Case 6	1912	29	M	Repeated attacks of pain in lower part of abdomen; large amount of blood by rectum with last attack; ileal intussusception with diverticulum at apex; resection	Died
Brennecke..... Case 3	1913	5	M	Attacks of abdominal pains, vomiting, and bloody stools; ileal intussusception with diverticulum at apex	Recovery
Brennecke..... Case 4	1913	9 mo.	M	Bloody stools; ileocecal intussusception with diverticulum and appendix in intussusceptum; resection	Died
Douriéz.....	1922	18	M	Abdominal pain, vomiting; blood in stool once; invagination of diverticulum in ileum; resection	Died
Stone, E.....	1923	1½	M	Bloody stools unmixed with mucus; gastric mucosa at tip of invaginated diverticulum; no intussusception; no ulcer of diverticulum found	Recovery
Schlutz.....	1926	3 mo.	Not stated	Slight bleeding by rectum; ileal intussusception containing a diverticulum, which was acutely inflamed and ulcerated; resection	Died
Montgomery.....	1928	2¼	F	Two bloody stools; ileal intussusception with diverticulum at apex; reduction; excision of portion of diverticulum	Died
Shanon..... Case 1	1928	4½ mo.	F	Frequent bloody stools; inverted diverticulum with an ileal intussusception; resection	Died
Doolin.....	1929	44	M	Bleeding by rectum; ileocolic intussusception with perforated invaginated diverticulum at apex; resection of intussusception and diverticulum	Recovery
Christopher.....	1930	9 mo.	M	Bleeding by rectum; ileocecal intussusception with diverticulum at apex; reduction; diverticulum not excised	Died
Hudson and Koplik.... Case 5	1932	7 wk.	M	Blood in stool; ileocolic intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Hudson and Koplik.... Case 8	1932	10½	M	Bleeding by rectum; ileocolic intussusception with diverticulum at apex; reduction; excision of diverticulum	Recovery
Hudson and Koplik.... Case 9	1932	7⅝	F	Blood in stool; ileocolic intussusception with diverticulum at apex; reduction; excision of diverticulum; gastric mucosa in diverticulum	Recovery
Hudson and Koplik.... Case 21	1932	½	M	Blood by rectum; ileocecal intussusception with diverticulum at apex; reduction; excision of diverticulum; gastric mucosa in diverticulum	Died
Hudson and Koplik.... Case 22	1932	½	M	Bleeding by rectum; ileo-ileocolic intussuception with diverticulum at apex; reduction; diverticulostomy	Recovery
Hudson and Koplik.... Case 27	1932	3¾	M	Blood in stool; inflammation of diverticulum; local peritonitis; obstruction probably from invagination of diverticulum; resection; gastric mucosa present in diverticulum	Died
McCann.....	1932	6	M	History of bleeding by rectum; constipation; pain in lower part of abdomen; invaginated diverticulum in lower part of ileum; excision; diverticulum lined with duodenal mucosa; pancreatic tissue found in muscle layer	Recovery

The case emphasizes that extremely severe acute symptoms including abdominal pain and bleeding from the rectum, unmixed with mucus, may occur in persons with Meckel's diverticulum without any evidence of invagination, intussusception or ulceration.

In this case, as in several previously reported (table 3), there was heterotopic tissue in the diverticulum, but the source of the bleeding could not be determined either at operation or microscopically. It is reasonable to suppose, however, that it must have come from the diverticulum, since hemorrhage did not recur after its removal (three years' follow-up).

Because our patient, together with others (table 3), exhibited symptoms similar to those recorded for the group who had bleeding associated with ulcer of a Meckel's diverticulum, we believe that the latter condition cannot be considered as a clinical entity.

Search for a Meckel's diverticulum should always be made when there is unexplained bleeding by rectum or peritonitis of undetermined origin, or when the operative findings are not in accord with the clinical diagnosis. The indication is to remove the diverticulum even though it may appear harmless, because the mortality is high after perforation or after acute pathologic processes set in. The mortality in thirty-five cases of perforated ulcer of Meckel's diverticulum was 42.5 per cent.

A person with a lesion of Meckel's diverticulum, especially if the lesion is bleeding peptic ulcer, may pass from a state of relatively good health to one of acute illness, collapse and shock with amazing rapidity. Sudden severe pain in the lower part of the abdomen with rigidity, signs of diffusing peritonitis, fever and leukocytosis, especially in children, should lead one to suspect a perforated Meckel's diverticulum.

Cryptic intestinal bleeding should always constrain one to suspect a Meckel's diverticulum as a possible source.

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PEPTIC ULCER

IX. CHRONIC LESIONS OF THE DUODENUM FOLLOWING EXPERIMENTALLY PRODUCED PYLORIC DYSFUNCTION

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Some demonstrable and appreciable dysfunction of the pylorus is often found in patients who have peptic ulcer, whether the ulcer is situated in the stomach or in the duodenum. The dysfunction is not a passive stenosis but an active disturbance of the normal rhythm of the pylorus. Roentgenologically and at the time of operation, various degrees of spasm, hypertonicity and occasionally even slight hypertrophy have been demonstrated so frequently that they are generally accepted as phenomena almost concomitant with peptic ulcer. For this reason atropine, which tends to relax the pylorus, has been used for a long time in the medical management of patients with peptic ulcer and not infrequently seems to be a real factor in the amelioration of symptoms and the control of certain forms of the disease.

Two conflicting theories concerning dysfunction of the pylorus in cases of peptic ulcer have been advanced. One is that the dysfunction is secondary, the result of the ulceration. The other hypothesis is that pyloric dysfunction in such cases is primary and therefore may have some bearing on the etiology of peptic ulcer.

Accordingly, the following procedures were devised to produce experimentally in dogs a pyloric dysfunction that might be studied to investigate the possible relationship between abnormal function of the pylorus and the formation of peptic ulcer. The animals were studied roentgenologically and by exploratory operation or necropsy at various intervals up to two years after the induction of pyloric dysfunction. The results are described in this report.

METHOD OF EXPERIMENTATION

The principle of the experimental method devised was the addition of what might be termed an accessory pylorus at the outlet of the stomach. This was accomplished by the transplantation of a segment of jejunal muscle with intact mesentery to encircle the otherwise normal and undisturbed pylorus. It was thought that an independently contractile ring of muscle might interfere with the normal rhythm of the pylorus and thereby cause pyloric dysfunction.

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Normal healthy dogs were used in all experiments, and for all operative procedures ether anesthesia and an aseptic technic were employed. No rubber-covered or other intestinal clamps and no unabsorbable sutures were used in any of the operations.

Through an upper midline incision the pylorus was exposed. By blunt dissection small openings in the gastrohepatic and the great omentum (there is no gastrocolic omentum in the dog) were made at the pyloric ring. These were made to permit the passage of a tape for traction and later a ring of transplanted muscle

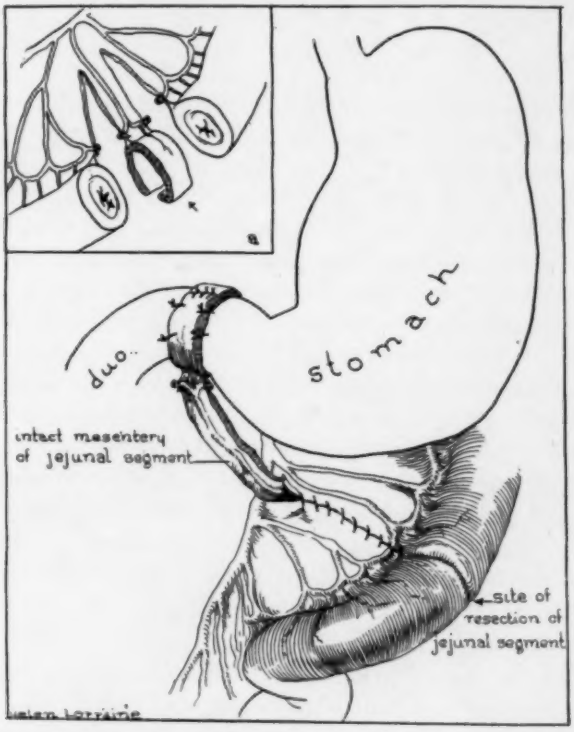

Fig. 1.—Diagram of operation for placing around the pyloric ring a segment of jejunal muscle with intact mesentery; *a*, method of preparing the segment of jejunum by resection, antimesenteric section and excision of the mucosa.

completely around the pyloric ring, in contact with its serosal surface and without interfering with the blood vessels and nerve connections in the region.

The jejunum, beginning at the ligament of Treitz, was examined until a segment with the desired characteristics was found. This segment, from 2 to 3 cm. in length, was supplied by a branch of the mesenteric vessels long enough to permit the approximation of the segment of intestine and the pylorus without tension and direct enough to permit the resection of the segment with intact mesenteric vascular and nerve connections. This segment was resected and the severed ends

of the jejunum adjacent to it were united by end-to-end anastomosis, thereby restoring the continuity of the gastro-intestinal tract.

The isolated, ringlike segment of jejunum with its mesenteric attachment intact was sectioned opposite the mesentery and its mucosa peeled away in a sheet, leaving a strip of muscle with independent circulation (fig. 1 *a*). The tape previously placed around the pylorus was used for traction and exposure, and an Allis forceps was passed behind the pylorus; one end of the strip of muscle was grasped by it and half of the strip pulled through. The tape was then withdrawn and the other half of the strip of muscle was folded over the anterior surface of the pylorus, and the two ends of the muscle were sutured together. The resulting ring of muscle was adjusted and held in place, immediately surrounding and overlying the pyloric ring, by a few interrupted sutures of fine catgut (fig. 1).

In the animals subjected to this operation a ringlike segment of jejunal muscle with intact mesenteric blood and nerve supply surrounded the pyloric ring throughout its entire circumference. Any independent contraction of the jejunal ring tended to close the pyloric orifice of the stomach in the same manner that contraction of the pyloric ring closed the orifice. Synchronous actions of the two rings were complementary, while asynchronous actions were in opposition to each other. In either instance the normal action and function of the pylorus were disturbed.

RESULTS

The operative mortality was not high, only one dog in eight succumbing to the immediate operative procedure. The state of nutrition and the general condition of the animals did not seem to be altered in any way, there being no loss of weight and no anorexia or weakness, even in the dog surviving for two years. During the course of the experiment one animal gave birth to and reared a litter of puppies uneventfully. No complications were observed except in two instances in which apparently some mucosal cells, which must have been incompletely stripped from the transplanted band of muscle, proliferated and formed a small cyst, filled with a cheesy material similar to that found in sebaceous cysts in man. It was interesting to see the apparent normality of the mucosa lining these cysts, even to the reproduction of intestinal glands.

Anatomic and Physiologic Observations.—Exploratory operations on the animals demonstrated that the transplanted ring of jejunal muscle had healed in place so well that it resembled a part of the pyloric ring itself. It had become "peritonealized" smoothly and appeared to be healthy. It seemed to derive part of its circulation from its original mesenteric vessels and part from the pyloric circulation with which it seemed to have anastomosed itself. Its mesentery had resolved itself into a "peritonealized" cylindric cord, in which the arterial pulsations were plainly visible and palpable. Microscopic examination of this cord revealed apparently normal vascular channels (fig. 2).

The jejunal ring was seen to contract frequently of its own accord. Also local stimulation of the ring itself or of its mesentery caused con-

traction of the muscle. When the muscle contracted there was a definite constricting action on the pylorus. It was noted, however, that the pyloric ring was relatively so much stronger than the jejunal ring that the latter could not seriously interfere with strong contractions of the pyloric muscle itself. Electrical stimulation of the wall of the intestinal ring caused violent contraction of the circular muscle fibers, while electrical stimulation of the mesentery caused contraction of the longitudinal muscle fibers of the intestinal ring.

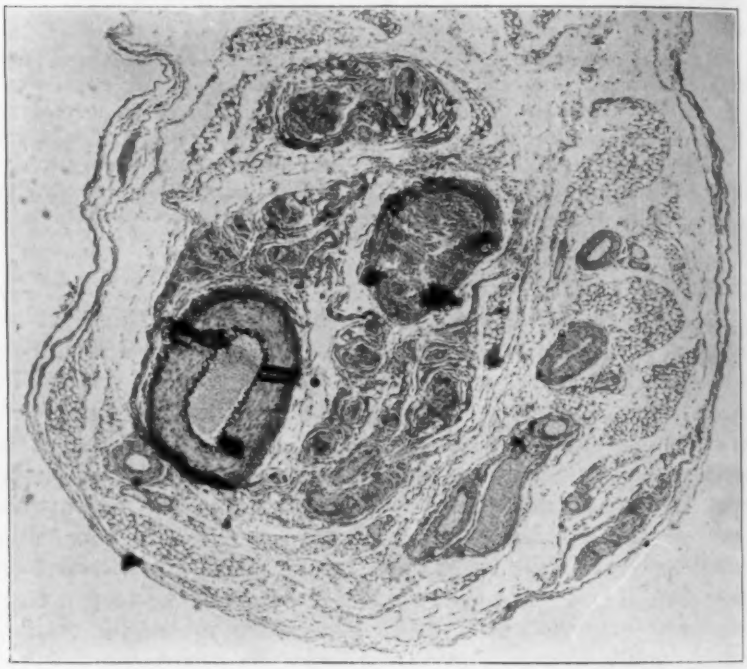

Fig. 2.—Photomicrograph of a section of the mesentery of the transplanted ring of the jejunum, with normal vessels; × 50.

Roentgenologic Observations.—The technic of the examinations was essentially the same as that described by me [1a] in a former report except that the contrast medium was a commercially supplied barium-cereal mixture. The dogs ate the meal readily, and it was satisfactory in every respect. Both fluoroscopic and roentgenographic examinations were made.

1a. Morton, C. B.: Observations on Peptic Ulcer: II. A Roentgenologic Study of Experimental Chronic Ulcer, Ann. Surg. **85**:222, 1927; V. Findings in Experimentally Produced Peptic Ulcer; Etiologic and Therapeutic Considerations, ibid. **87**:401 (March) 1928.

The observations on the animals of the experiment were controlled by similar observations on the same animals preoperatively and on other normal animals on which no operation had been performed. In the normal dog the stomach emptied with a certain degree of regularity and rhythm until it was completely empty in from three to four hours.

In the animals with a transplanted jejunal ring around the pylorus, however, the emptying was much less regular and rhythmic. The stomach appeared somewhat dilated and more bulbous than normal. In all instances the pylorus seemed to offer a definite resistance to rhythmic

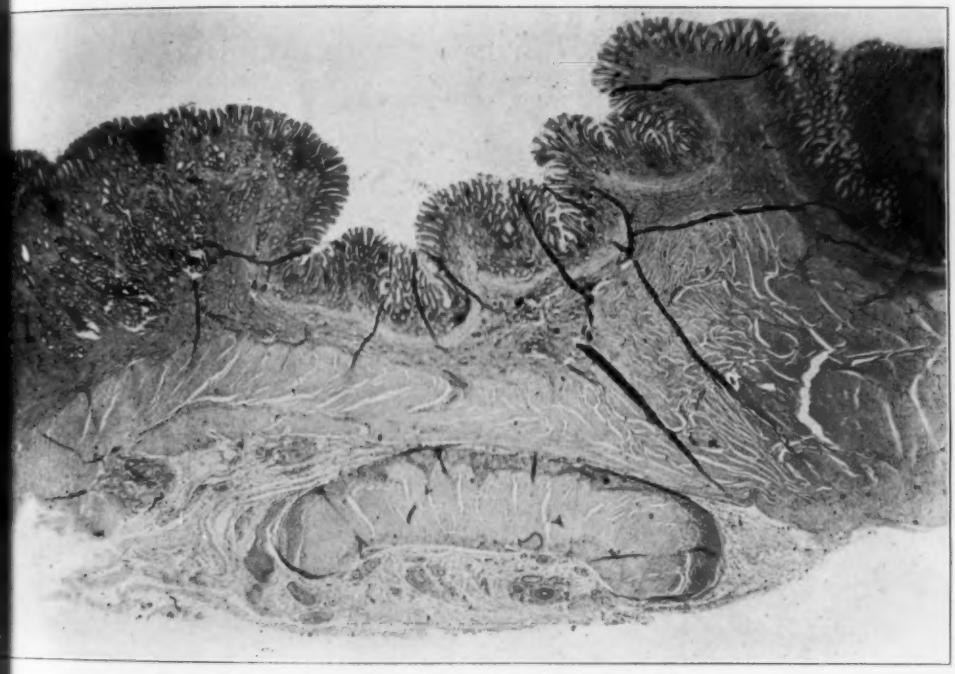

Fig. 3.—Photomicrograph of a section through the pylorus showing the transplanted ring of jejunal muscle; reduced from a magnification of 10. Note the definite evidence of duodenitis to the left of the pylorus.

emptying of the stomach. At the end of four hours there was an appreciable residue of the contrast medium in the stomach. No ulcerations of the duodenum or stomach were demonstrated. In general, the roentgenologic characteristics of the animals of the experiments were somewhat similar to the roentgenologic abnormalities found in patients with pylorospasm and other similar pyloric dysfunctions.

General Observations.—No gross ulceration of the duodenum or stomach was found in any experiment but in every one of them there

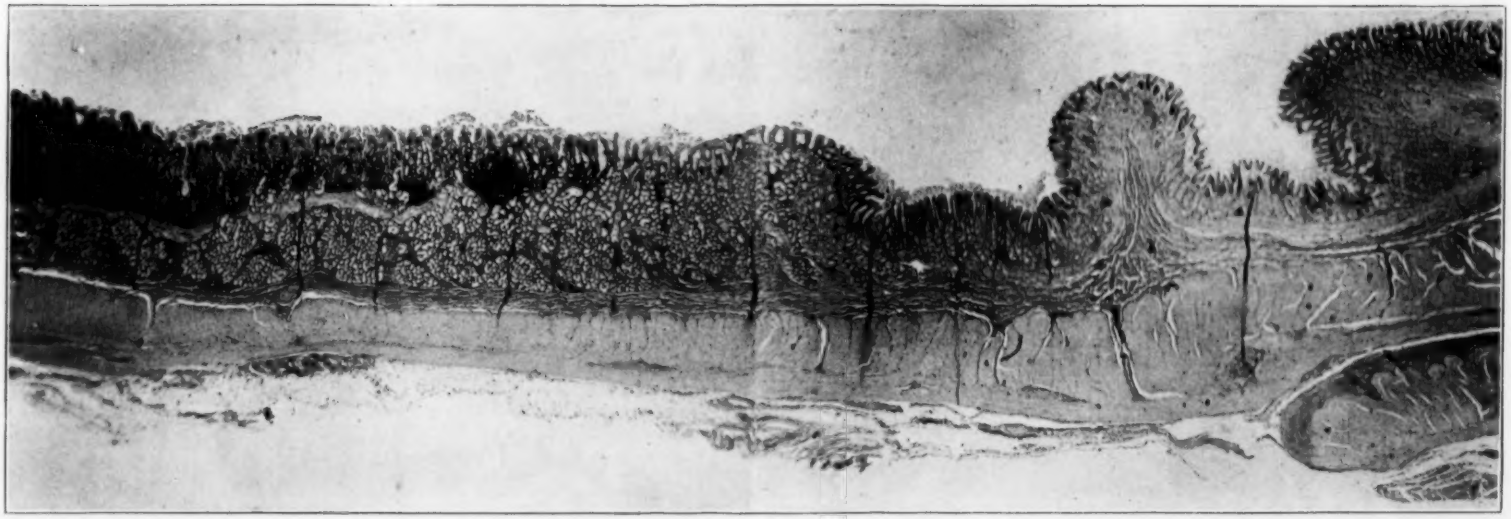

Fig. 4.—Photomicrograph of a section of the duodenum, pylorus and a small part of the stomach, showing a portion of the transplanted ring of the jejunal muscle at the extreme right of the section. Note the areas of lymphocytic infiltration, especially to the left of the center; reduced from a magnification of 10.

was gross and microscopic evidence of duodenitis (table). In an equal number of dogs used as controls no evidence of duodenitis was discovered. Some of the controls were normal animals on which no operation had been performed; others had had an abdominal incision with handling of the stomach and duodenum and others had undergone operations on the biliary tract in the course of other experiments.

The gross evidence of duodenitis in the animals of the experiments was not marked. No apparent serosal stippling and no marked thickening of the wall of the duodenum were seen. Inside the lumen, however, the mucosa frequently had a slightly eroded and definitely reddened appearance.

Data of Seven Experimental and Seven Control Animals

Dog	Operation	Date of Operation	Observation, Date	Results, Gross and Microscopic	Duration of Experiment
1	Jejunal band around pylorus	Jan. 14, 1930	Exploration, Jan. 16, 1933	No ulcer Duodenitis	2 years
2	Jejunal band around pylorus	Oct. 31, 1929	Exploration, Jan. 31, 1930	No ulcer	3 months
			Necropsy, May 30, 1930	Duodenitis	7 months
3	Jejunal band around pylorus	Oct. 29, 1929	Exploration, Jan. 31, 1930	No ulcer	3 months
			Necropsy, Feb. 13, 1930	Duodenitis and gastritis	3½ months
4	Jejunal band around pylorus	June 19, 1930	Necropsy, Feb. 26, 1931	Duodenitis	8 months
5	Jujenal band around pylorus	June 18, 1930	Necropsy, Feb. 26, 1931	Duodenitis	8 months
6	Jejunal band around pylorus	June 20, 1930	Necropsy, Feb. 26, 1931	Duodenitis	8 months
7	Jejunal band around pylorus	April 9, 1931	Necropsy, June 22, 1932	Duodenitis	14½ months
Seven control animals	Undisturbed gastro-intestinal tract	Tissue examined grossly and microscopically		Normal duodenum and stomach	

Microscopic examination of the tissue revealed changes similar to those characteristic of duodenitis in man. These consisted of various degrees of superficial mucosal erosions, infiltration of the mucosa and submucosa with lymphocytes, polymorphonuclear leukocytes and plasma cells, congestion of the capillaries, slight edema and fibrosis, evidence of apparently increased glandular epithelial activity and, last but most striking, various-sized collections of lymphocytes (figs. 3, 4, 5 and 6). The degree of duodenitis varied in proportion to the duration of the experiment. Lymph follicles, which are found normally in the duodenum of the dog, were seen in sections of the duodenum of the normal control animals. These follicles, however, were different from the collections of lymphocytes found in the duodenum of the animals of the experiments.

COMMENT

Judd and Nagel [1b] and Kirklin [2] have described the clinical features of duodenitis. The relationship of duodenitis and gastritis to duodenal and gastric ulcer has been thoroughly studied by Wellbrock,[3] who cited

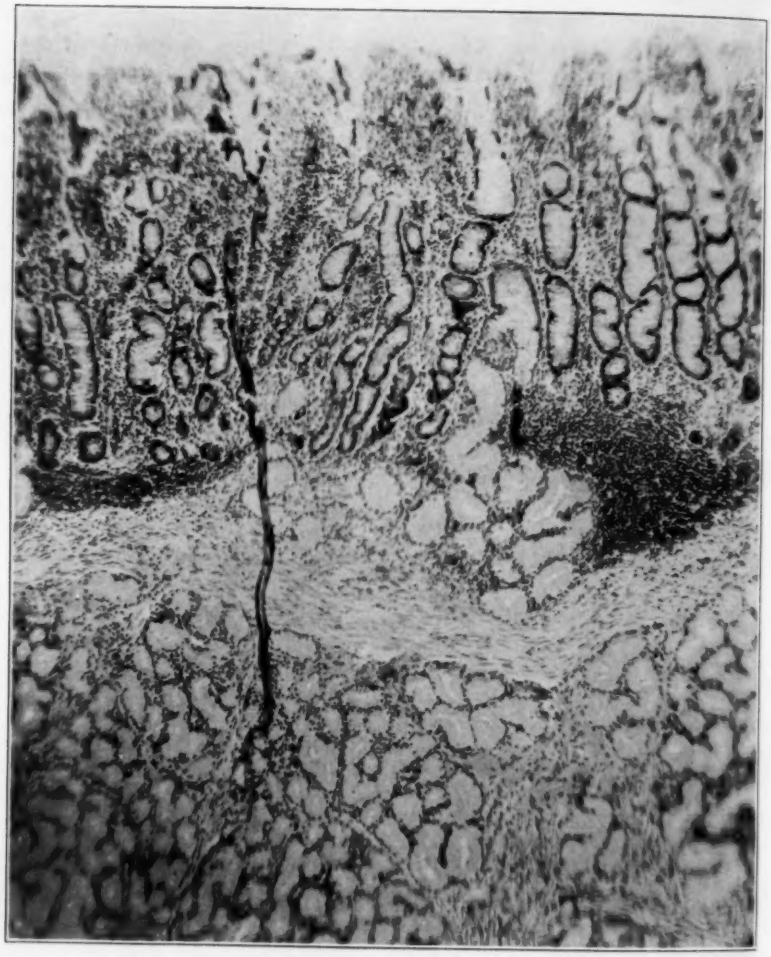

Fig. 5.—Photomicrograph showing collections of lymphocytes and generalized lymphocytic infiltration of the tissue in an area of duodenitis; reduced from a magnification of 75.

1b. Judd, E. S., and Nagel, G. W.: Duodenitis, Ann. Surg. **85**:380 (March) 1927.

2. Kirklin, B. R.: A Roentgenologic Consideration of Duodenitis, Radiology **12**:377 (May) 1929.

3. Wellbrock, W. L. A.: Duodenitis and Duodenal Ulcer, Ann. Surg. **91**:533 (April) 1930.

also similar considerations by Hauser,[4] Konjetzny,[5] and Konjetzny and Puhl.[6] As stated by Wellbrock, in many cases of duodenal ulcer in which clinical symptoms and roentgenograms are indicative of ulcer, a definite ulceration cannot be found at operation. Instead duodenitis is demonstrated. It is described as occurring in various forms, as simple duodenitis, duodenitis with erosion and ulceration, chronic duodenitis and healed ulcerated duodenitis. There are lymphocytes, polymorphonuclear leukocytes, plasma cells and a few eosinophils with congestion of the capillaries in the mucosa of the duodenum. In the more advanced chronic types the inflammatory reaction manifests itself by distinct hyperplasia of Brunner's glands, with infiltration of scattered lymphocytes and collections of lymphocytes throughout. The muscularis propria also contains some fibrous connective tissue. The blood vessels are sclerosed, the sclerosis increasing with the chronicity of the condition. The frequent association of the aforementioned changes characteristic of duodenitis with duodenal ulcer suggests a definite relationship between the two, duodenitis in all probability frequently preceding the formation of a peptic ulcer.

Comparison of the microscopic characteristics of duodenitis in man with the microscopic changes in the duodenum of the animals of the experiments demonstrates a close similarity between them. Analysis of the conditions of the experiments indicates several features that should be stressed.

The experiments were made in the dog, an animal in which spontaneous peptic ulcer occurs only with extreme infrequency. Acute ulcerations made experimentally in dogs heal with great rapidity. Chronic ulcerations have not been made experimentally in dogs with any consistency except by procedures which divert the alkaline juices in the duodenum away from that portion of the intestine into which the stomach empties, as for instance in experiments with surgical duodenal drainage.

Furthermore, the experimental procedures apparently affected directly only one very limited part of the gastro-intestinal tract, the pylorus. But the importance of that small ring of muscle may be more thoroughly appreciated when one considers the control which it must

4. Hauser, G.: Ueber die Beziehungen der chronischen Gastritis und Duodenitis zum chronischen Magen-und Duodenalgeschwür, Med. Klin. **23**:120 (Jan.) 1927.

5. Konjetzny, G. E.: Entzündliche Genese des Magen-Duodenalgeschwürs: Ein Beitrag zur Kenntnis der Aetiologie, Pathogenese und Therapie des Magen-Duodenalgeschwürs, Arch. f. Verdauungskr. **36**:189, 1925.

6. Konjetzny, G. E., and Puhl, H.: Ueber die Bedeutung der Gastritis und Duodenitis für die Entstehung des Magen-und Duodenalgeschwürs, Med. Klin. **23**:986, 1927.

exert over the emptying of the stomach, the regurgitation of material from the duodenum into the stomach and hence neutralization of the acid gastric chyme by the alkaline duodenal juices.

The experimentally produced alteration in the function of the pylorus was not the production of a rigid unyielding stenosis, such as

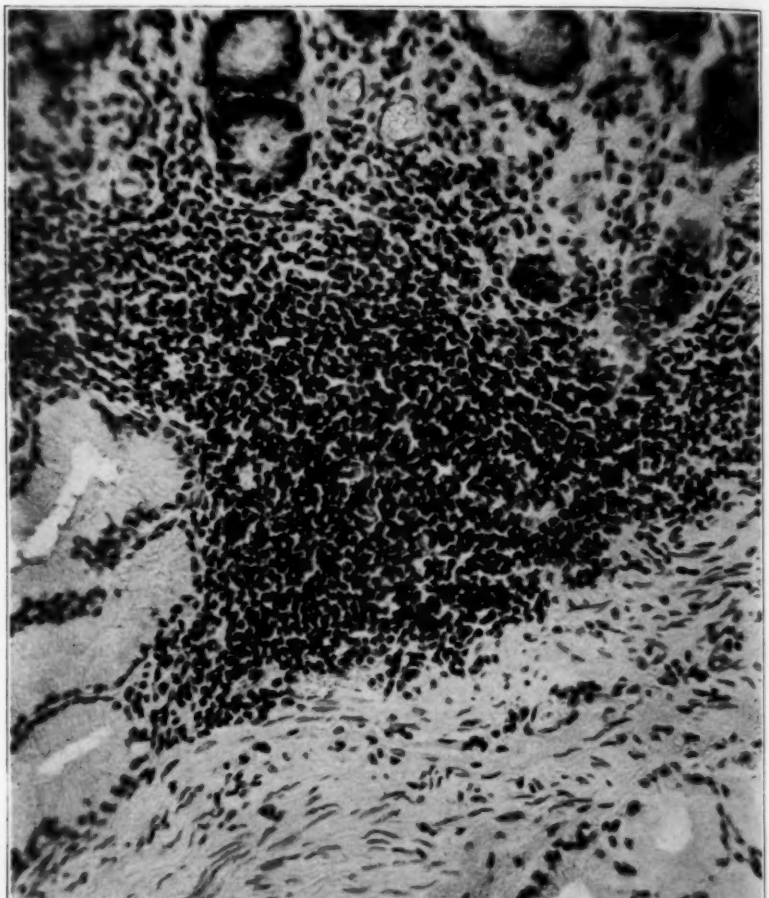

Fig. 6.—Photomicrograph of a collection of lymphocytes and other cells in an area of duodenitis; reduced from a magnification of 250.

might be caused by placing a rigid band around the pylorus. Rather, the experiment produced an altered function by interfering with the rhythm of the pylorus or getting it "out of step." It did not prevent complete opening of the pylorus, nor did it prevent complete closure,

but it prevented the opening and closing of the pylorus as it would normally open and close in response to the usual stimuli. The interference was demonstrated both by direct observation and by roentgenologic examination.

It could be seen that the abnormal pyloric function interfered with emptying of the stomach, and therefore it seems fair to assume that it interfered likewise with regurgitation and hence with orderly neutralization of the acid gastric chyme. Had the transplanted band of contractile muscle been able to exert a force equal to that of the powerful pyloric ring, more profound alteration in pyloric function might have ensued.

The demonstrable pyloric dysfunction of the experiments was followed by the formation of a chronic inflammatory lesion of the duodenum which, though not an actual peptic ulceration, is generally considered a closely related pathologic change. If one assumes that the altered pyloric function interfered with normal neutralization of the acid gastric chyme by the alkaline juices in the duodenum, one has a factor similar to, though of course not so potent as, that which with great consistency causes chronic peptic ulcers following the diversion of the alkaline juices by surgical duodenal drainage. Mann and Williamson [7] and I [8] have reported various experiments of this character.

In a series of cases previously reported by me,[9] simultaneous analyses of the contents of the stomach and duodenum were made in normal persons and in patients with peptic ulcer. The results indicated appreciably less complete prepyloric and postpyloric neutralization of the acid chyme in patients with peptic ulcer than in normal persons. This variation seemed most probably due to a difference in the action of the pylorus in the two groups.

The importance of the pylorus in relation to duodenitis and duodenal ulcer has been demonstrated clinically by Judd and Nagel, Horsley [10] and Martin and Burden.[11] They have shown that resection of a portion of the pyloric muscle is a satisfactory and effectual means of bringing about healing of both duodenitis and duodenal ulcer.

7. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

8. Morton, C. B.: Observations on Peptic Ulcer: II. A Roentgenologic Study of Experimental Chronic Ulcer, Ann. Surg. **85**:222, 1927; V. Findings in Experimentally Produced Peptic Ulcer: Etiologic and Therapeutic Considerations, ibid. **87**:401 (March) 1928.

9. Morton, C. B.: Observations on Peptic Ulcer: VI. Preliminary Report of Clinical Experiments with Gastro-Duodenal Analysis, Am. J. M. Sc. **177**:65 (Jan.) 1929.

10. Horsley, J. S.: A New Operation for Duodenal and Gastric Ulcer, J. A. M. A. **73**:575 (Aug. 23) 1919.

11. Martin, E., and Burden, V. G.: Pyloric Achalasia and Peptic Ulcer, Ann. Surg. **88**:565 (Sept.) 1928.

CONCLUSIONS

In conclusion, the results of the experiments, in which a degree of alteration in the normal function of the pylorus was produced by encircling the pyloric ring with a contractile band of jejunal muscle, seem to indicate that primary pyloric dysfunction may cause chronic inflammatory lesions of the duodenum. In the dog the lesion is a duodenitis which is almost identical with duodenitis in man. Because of the definite relationship between duodenitis and duodenal ulcer clinically, the probable significance of the results as regards the etiology of peptic ulcer in man is at least suggestive.

SIGNIFICANCE OF ANAEROBIC ORGANISMS IN PERITONITIS DUE TO LIVER AUTOLYSIS

BACTERIAL FLORA OF THE LIVER AND MUSCLE OF NORMAL DOGS

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The recent investigations of Ellis and Dragstedt [1] have reopened the question of the bacterial flora of normal living tissue. They found a gram-positive anaerobic bacillus present in the liver of normal dogs and in the peritoneal exudate of dogs dying from intraperitoneal autolysis of fresh liver and sterile liver. Andrews and Hrdina,[2] while doing research work in connection with the same problem, found toxic strains of Clostridium welchii in the peritoneal exudate of dogs dying of liver peritonitis. They also refer to the liver organism as Bacillus welchii. The organism that these workers recovered produces a filtrate which, in large doses, is lethal for guinea-pigs and rabbits. Rewbridge [3] found B. welchii in the peritoneal exudate formed from injections of bile and bile salts and assumed it to be the agent in death from this cause.

The bacterial flora of killed animal tissue has been studied by many investigators, but the findings cannot be considered as typical of living animal tissue. Wolbach and Saiki [4] in 1909 studied the bacterial content of the livers of twenty-three living dogs. They found a gram-positive anaerobic spore-bearing bacillus present in twenty-one of twenty-three livers which was similar to, but not identical with, B. welchii. Reith [5] cultured the muscle and blood of living animals and found that of 108 samples from healthy dogs, rabbits and guinea-pigs, the muscular tissues were 83 per cent positive and the blood 84 per cent positive for bacteria

From the Research Division, Indiana University School of Medicine.

1. Ellis, J. C., and Dragstedt, L. R.: Liver Autolysis In Vivo, Arch. Surg. **20**:8 (Jan.) 1930.

2. Andrews, E., and Hrdina, L.: The Cause of Death in Liver Autolysis, Surg., Gynec. & Obst. **52**:61 (Jan.) 1931.

3. Rewbridge, A. G.: Etiological Rôle of Gas-Forming Bacilli in Experimental Bile Peritonitis, Surg., Gynec. & Obst. **52**:205 (Feb.) 1931.

4. Wolbach, S. B., and Saiki, T. A.: A New Anaerobic Spore-Bearing Bacterium Commonly Present in the Livers of Healthy Dogs, J. M. Research **21**:267, 1909.

5. Reith, A. F.: Bacteria in Muscular Tissues and Blood of Apparently Normal Animals, J. Bact. **12**:367 (Nov.) 1926.

of various types. Berg, Zau and Jobling [6] found the animal liver to contain an anaerobe with the same characteristics as the organism described by Wolbach and Saiki, but found bile and blood to be uniformly sterile.

In view of some differences in results when the work of Andrews and Hrdina was repeated in this laboratory, we have attempted to ascertain if toxic strains of C. welchii regularly inhabit the liver of healthy dogs and if the same organisms are present and cause death in in vivo autolysis of liver. To this end we have studied the livers of sixteen normal healthy dogs and the muscle tissue from six dogs and present a preliminary paper on a cultural study of the organisms found.

METHOD OF OBTAINING SPECIMENS

Stock dogs were given injections of morphine and atropine one hour previous to the operation. The abdomen was shaved, scrubbed with soap and water, washed thoroughly with ether and painted with iodine. Ether was used for anesthesia; the dogs were well draped with sterile linen. The operation was started with the surgeon wearing two pairs of gloves. The skin of some of the first dogs operated on was cut with a knife, but all the cultures obtained in this manner were contaminated with Staphylococcus and Streptococcus. It was found that if the skin was opened with a hot wire cautery, cultures did not contain these organisms. The final technic was as follows: The skin and fascia were opened with the cautery, the muscle was split with the fingers to eliminate bleeding, and the peritoneum was grasped in four Allis clamps and pulled out of the wound before cutting. At this stage the operator's first gloves were removed as a final precaution, and the presenting lobe of the liver was grasped in a large Kocher clamp. A freshly sterilized knife or the cautery was used to remove a few grams of liver around the point of the clamp, and the specimen was dropped into the culture mediums. The cut surface of the liver was sewed with black silk, the omentum was pulled down and tied to the operative site and the dog was returned to the pen.

We have spent ten months in the study and cultivation of known pure cultures of the Clostridium group, in the preparation of suitable and differential culture mediums and in the selection of methods of growth. We have studied three known toxic strains of C. welchii, two strains of Clostridium tetani, one strain of Clostridium edematis maligni and one strain of Clostridium putrificum. We have used a strain of C. welchii as a control for every cultural method used in growing the organisms isolated from tissue.

CULTURAL METHODS

We have found that good growth of all anaerobic organisms studied may be had in veal infusion meat medium in open test tubes without the aid of petrolatum or paraffin. One pound of lean ground veal to each liter of distilled water is infused in an icebox for twenty-four hours. After heating at 55 degrees for one hour the meat is filtered out, pressed and placed to a depth of from 2 to 3 inches

6. Berg, B. N.; Zau, Z. D., and Jobling, J. W.: Bactericidal Function of the Liver, Proc. Soc. Exper. Biol. & Med. **24**:433 (Feb.) 1927.

(5 cm. to 7.6 cm.) in large test tubes or Erlenmeyer flasks which are put in the autoclave for one hour and a half at 15-pound pressure. The broth is enriched to 1 per cent with peptone and to 0.5 per cent with sodium chloride, boiled five minutes and filtered. The clear broth is then titrated to p_H 8.0 and is boiled again for ten minutes. It is filtered again, distributed into the tubes containing the meat and sterilized in an Arnold sterilizer for one hour and a half on three successive days. Freshly ground dog liver is treated in the same manner for cultivation of liver organisms. For the production of exotoxins, fresh dog blood serum previously filtered through a Berkefeld candle is added to the veal medium, up to 10 per cent. The ground meat medium furnishes sufficient anaerobiosis to give good growth of all organisms studied.

Deep agar colonies for isolation of organisms are obtained in 1 per cent veal infusion agar or 1 per cent liver infusion agar grown in Burri tubes as modified by Hall.[7]

Surface agar colonies are grown in tubes devised in this laboratory, on various modifications of 3 per cent liver and 3 per cent veal infusion agar. Rabbits' blood, dried ox blood, hemoglobin and various sugars were used as enriching agents. Sodium sulphite agar, as reported by Wilson and Blair,[8] was used for differentiation. C. welchii and the organisms isolated from the dog muscle have been found to grow abundantly in jars of pure carbon dioxide under pressure. Neither the organism from the liver nor any of the other anaerobes studied would grow in this way in pure culture.

A veal meat infusion medium was used for all initial cultures, for subcultures after heating and for all stock cultures. Spore-forming organisms will remain alive in tubes of this medium for months.

ROUTINE FOR CULTURING SPECIMENS

Tubes containing the fresh liver obtained at operation were incubated at 40 C. for twenty-four hours. Rapid growth and the formation of much gas always resulted. A subculture was made into the same medium and the original culture was heated in a water bath to 80 C. for fifteen minutes, in order to kill all vegetative forms. Heating invariably resulted in a rapid increase in gas production to the point that the cultures appeared to be boiling. Another subculture was made after heating, and both subcultures were incubated for another twenty-four hours. Dilutions of the growing, heated culture were made in ordinary dextrose broth and as few organisms as possible transferred to a Burri tube. These tubes were incubated and frequently observed; they were removed when colonies appeared. The colonies were studied morphologically and transferred again to the stock medium, from which surface agar inoculations were made.

All inoculations of differential mediums were made from previously heated cultures. All were repeatedly picked from colonies in the Burri tubes which were widely separated or from distinct colonies on surface agar.

Fermentation reactions were obtained in 1 per cent liver agar to which the various sugars and Andrade's indicator had been added

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7. Hall, I. C.: An Improved Technic in Burri's Method of Isolating Obligately Anaerobic Bacteria, Am. J. Pub. Health **20**:536 (May) 1930.

8. Wilson, W. J., and Blair, E. M. M'V.: The Application of Sulphite-Glucose-Iron Agar Medium to the Quantitative Estimation of B. Welchii and Other Reducing Bacteria in Water Supplies, J. Path. & Bact. **27**:119 (Jan.) 1924.

RESULTS

Using the technic described, we have studied the livers of sixteen normal dogs. All specimens weighed approximately 4 Gm. and were removed in each case from the left lobe adjacent to the gallbladder. All specimens yielded a thermophilic anaerobe which we describe as "dog liver organism 1." As shown by the morphology and cultural charac-

Morphologic and Cultural Observations

	Clostridium Welchii*	Dog Liver Organism 1	Dog Muscle Organism 1
Morphology	In liquid medium, uniform short fat rods with truncated ends growing singly and in pairs; in 10 to 14 hour cultures bacilli very short, becoming longer until 4 to 6 microns long, granular, with irregular broken outlines at 72 hours	In liquid medium, long and short bacilli, slender, curved or wavy; no constant size or shape; ends square; grow in masses and long chains; longer and more variable in shape than the Welch bacillus	Large bacilli uniform in size with rounded ends; no tendency to curved forms; uniformity of organisms more pronounced in surface agar colonies; bacilli larger than B. welchii
Staining	Constantly G+ in young liquid cultures; G— in old cultures with staining variations in a single organism; agar colonies variable even in young cultures	Variable from earliest culture; predominance of G— forms in all cultures; granular forms usually predominate in old cultures	Stain a deep dark blue with little tendency to G— forms when growing in colonies; G+ and G— forms seen with equal frequency in liquid cultures
Motility	Nonmotile; encapsulated	Nonmotile; no capsule	Nonmotile; no capsule
Pathogenicity	Intramuscularly in pigeons: 1 cc. toxin dil. 1:4, death, 12 hours; 1 cc. toxin dil. 1:6, death, 24 hours	Intramuscularly in pigeons (average size): 1 cc. toxin dil. 1:4 in sodium chloride, harmless; 1 cc. toxin undil., harmless	Intramuscularly in pigeons: 1 cc. toxin undil., harmless
	Intraperitoneally in guinea-pigs (medium size): 1 cc. toxin undil., death; 6 hours; 2 cc. toxin undil., death, 3 hours	Intraperitoneally in guinea-pig (medium size): 6 cc. toxin undil., harmless	Intraperitoneally in guinea-pig (medium size): 2 cc. toxin undil., no harm; 6 cc. toxin undil., no harm
	Intraperitoneally in dogs: 35 cc. of a whole broth culture filtered to remove meat particles, death in 72 hours	Intraperitoneally in dogs: 35 cc. whole broth culture, meat free, harmless	

* Cultural characteristics of C. welchii are included for purposes of comparison.

teristics which we record in detail, this organism is not C. welchii and does not closely resemble it.

On two occasions we have incubated large masses of dogs' liver, keeping the left lobes separate from the right. In these instances we have found anaerobes other than organism 1. The bacterial content of the left lobes when incubated in large masses is more profuse than the right. Clostridium sporogenes and organisms of the Clostridium group which more closely resemble the Welch bacillus were found in the left lobe. In every case, however, they differed in sugar fermentation and pathogenicity. These organisms regularly ferment mannitol, inulin,

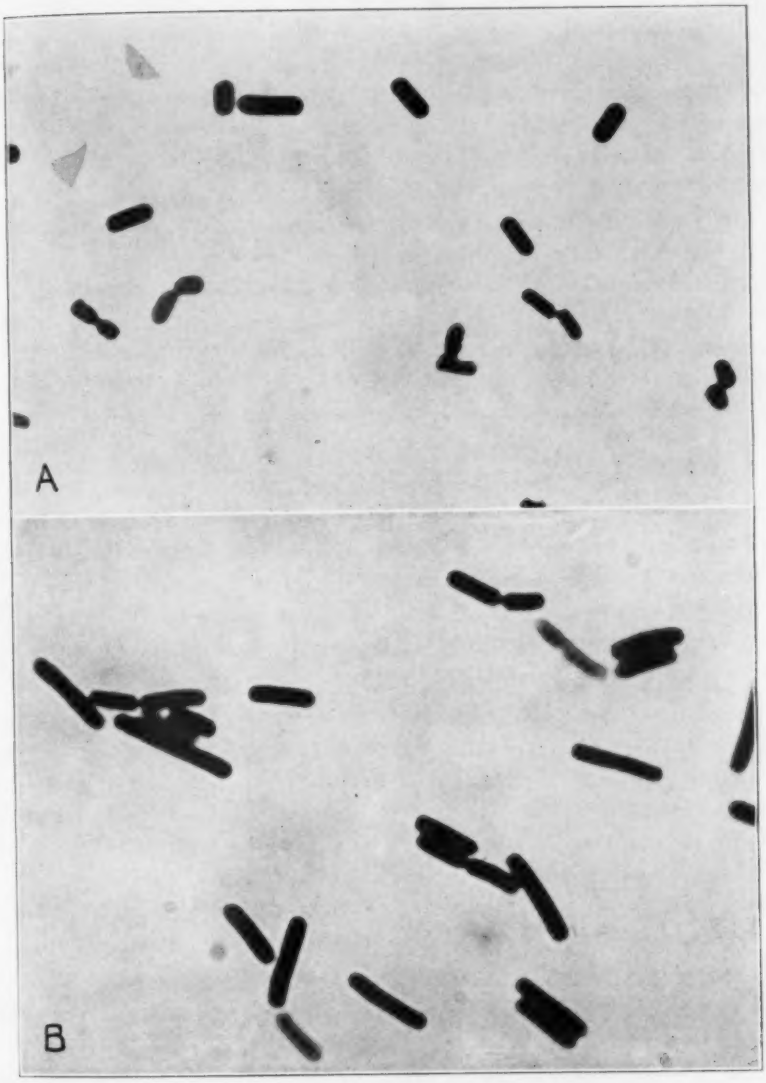

Fig. 1.—*A*, C. welchii in a twelve hour liquid culture in veal infusion meat medium; *B*, C. welchii in an eighteen hour surface colony on liver infusion blood agar under carbon dioxide.

glycerin, starch, sorbite and dulcitol. We were unable to demonstrate an exotoxin, nor were the organisms pathogenic when the whole organism was injected into a guinea-pig's muscle in young broth cultures.

Owing to our inability to insure strict bacteriologic technic in removing large masses of liver, we give no detailed descriptions of these occasional organsims. We strongly suspect that the bacterial flora of the dog's liver varies with different lobes, also varying in different animals and in the same animal at different times. However, the organism which we describe in detail as dog liver organism 1 has been found constantly present in the livers of sixteen normal dogs.

In studying dog muscle tissue, we have used a technic similar to that for liver. The skin was opened with a cautery, and 2 to 3 Gm. samples were taken. One sample of a dog's right rectus muscle was sterile; two samples of right rectus muscle and three other samples contained a strain of anaerobic bacilli differing from the liver organism and from C. welchii. A detailed description of this organism will be found in the table under the heading "Dog Muscle Organism 1."

C. Welchii on Veal Infusion Mediums.—Gas bubbles appear in from six to eight hours after the inoculation. The gas increases rapidly in amount until at the end of twenty-four hours the meat is infiltrated with gas and rises to the top of the liquid. The broth below is homogeneously clouded. Gas production becomes feeble after ninety-six hours, but occasional bubbles arise in this medium after standing for months at room temperature. There is no digestion of the meat, and the odor of these cultures is not unpleasant.

Organisms from Dog Liver on Veal Infusion Meat Mediums.—Gas bubbles in the subcultures do not appear for from seventy-two to ninety-six hours. Growth is then evident by a feeble production of gas which increases somewhat, but which never becomes rapid. The meat is never raised. Growth continues indefinitely; however, at the end of from seven to ten days the meat in the tubes is darkened and reduced to a mushy slime with a putrefactive and very offensive odor. The broth above the meat is at all times clear and is somewhat darkened.

Organisms from Dog Muscle on Veal Infusion Meat Mediums.—Gas appears in twenty-four hours and increases rapidly. The meat becomes infiltrated with the gas and rises to the top. The broth is milky. A fine white sediment accumulates in the bottom of the tube. Production of gas continues for forty-eight hours, and the meat falls to the bottom. At the end of six or seven days the meat is thoroughly digested and can be squeezed through fine cheesecloth. The cultures have a definitely putrefactive odor.

Colonies of C. welchii on surface agar usually appear to be raised, with an undulating surface and slightly irregular or crenated edges.

Fig. 2.—*A*, C. welchii in a thirty-six hour surface agar colony on heart infusion blood agar under illuminating gas; *B*, C. welchii in a seventy-two hour surface colony on sodium sulphite agar in an anaerobic tube.

They are opaque, moist and glistening. In deep agar, the colonies are round and white, solid at first, until after from eight to ten hours the presence of gas bubbles distorts the characteristic picture and colony formation is lost.

On surface agar, the liver organisms form flat, oval, scaly colonies with irregularly advancing edges. The surface is uneven and dry, and the colonies are yellow. In deep agar, the colonies appear as biconcave disks that are white with fuzzy outlines.

On surface agar, the colonies of the organisms found in muscle are rounded and droplike, with a moist, glistening surface. The surface is smooth. The edges are even and creamy yellow. In deep agar, the organisms grow diffusely through the medium.

Sodium Sulphite Agar.—C. welchii and other pathogenic anaerobes form black pigment on this medium. Grown in our anaerobic tubes, surface agar colonies of the Welch organism appear as black, shiny, raised dots in from eighteen to twenty-four hours. Deep agar and surface colonies of anaerobes from the dog's liver and muscle fail to form pigment at any time on this medium.

Sugar Fermentation.—Brown,[9] in a comprehensive study of anaerobic bacteria, has shown the variability of sugar fermentation even within a single strain. He concludes that anaerobes are divided into groups according to their ability to ferment sugars and according to their proteolytic powers, but that they cannot be rigidly divided as being either saccharolytic or proteolytic. We have found that C. welchii regularly ferments dextrose, sucrose, maltose and lactose with acid and gas, and that its proteolytic powers are very limited. Liver organisms have been found to ferment dextrose, lactose, starch, galactose and levulose, never sucrose and occasionally maltose. They have, however, the power of rapid proteolysis. Organisms from muscle form acid and gas in dextrose, lactose, maltose, inulin, starch, galactose, levulose, sucrose and mannitol. The proteolytic powers of these anaerobes are pronounced.

Pathogenicity.—In estimating the production of toxin of C. welchii the usual test methods were used. The cultures were made in veal infusion meat mediums to which fresh dog serum had been added up to 10 per cent. The toxin content was highest at forty-eight hours. Cultures were passed through a Berkefeld candle, and the resultant filtrate was tested by intramuscular injection into pigeons. Our cultures of C. welchii varied in toxicity, but all formed toxins to some degree, the highest testing 1:7 when diluted in physiologic solution of sodium chloride; that is, 1 cc. of a 1:7 dilution in physiologic solution of sodium

9. Brown, J. H.: A Study of Anaerobic Bacteria, J. Bact. **10**:513 (Nov.) 1925.

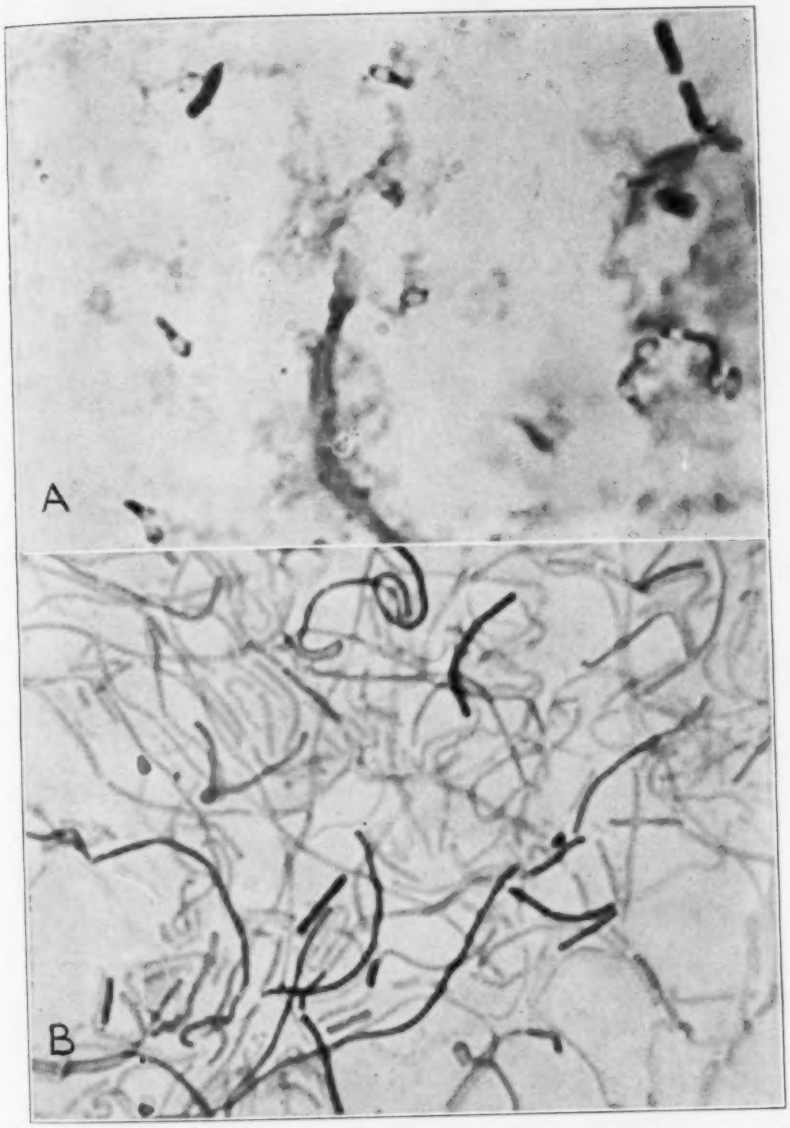

Fig. 3.—*A*, liver organism in a twenty-four hour liquid culture in veal infusion meat medium (note the spores); *B*, liver organism in a fourteen day surface colony on 1 per cent dextrose liver agar in an anaerobic tube.

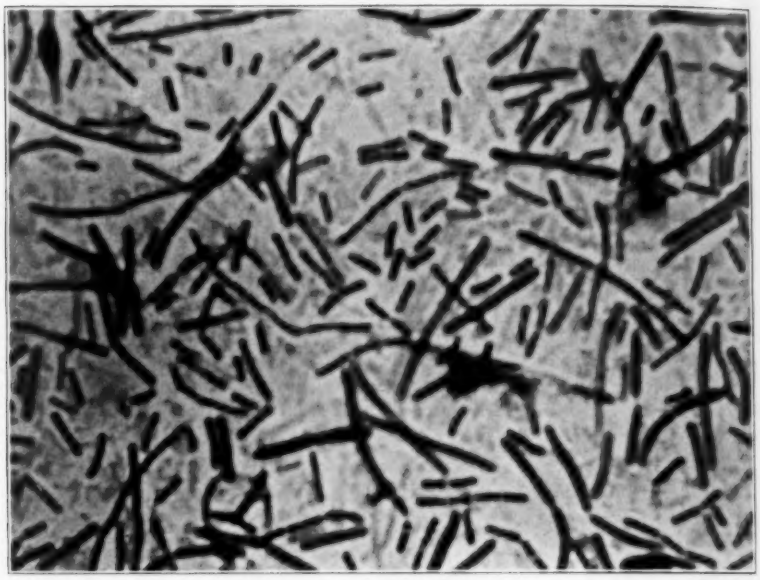

Fig. 4.—Liver organism in a seven day deep agar colony in 1 per cent dextrose, 1 per cent liver agar in Burri tube.

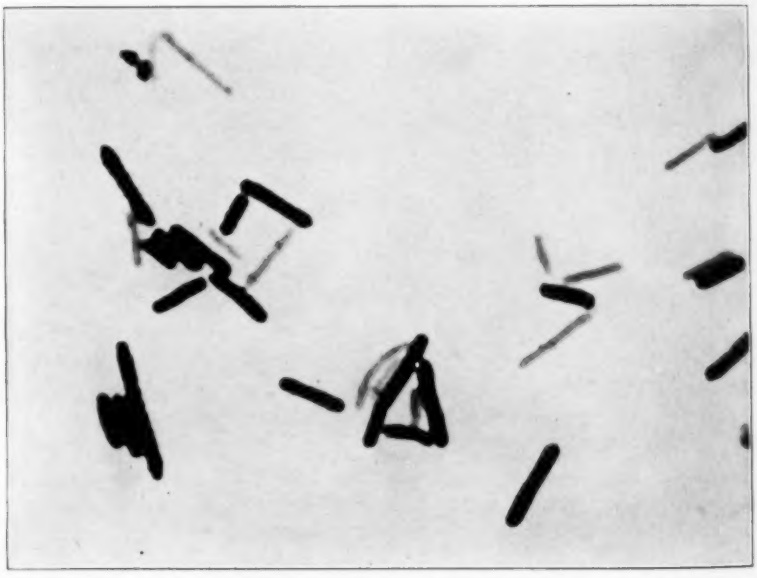

Fig. 5.—Muscle organism in a thirty-six hour surface colony on liver agar under carbon dioxide.

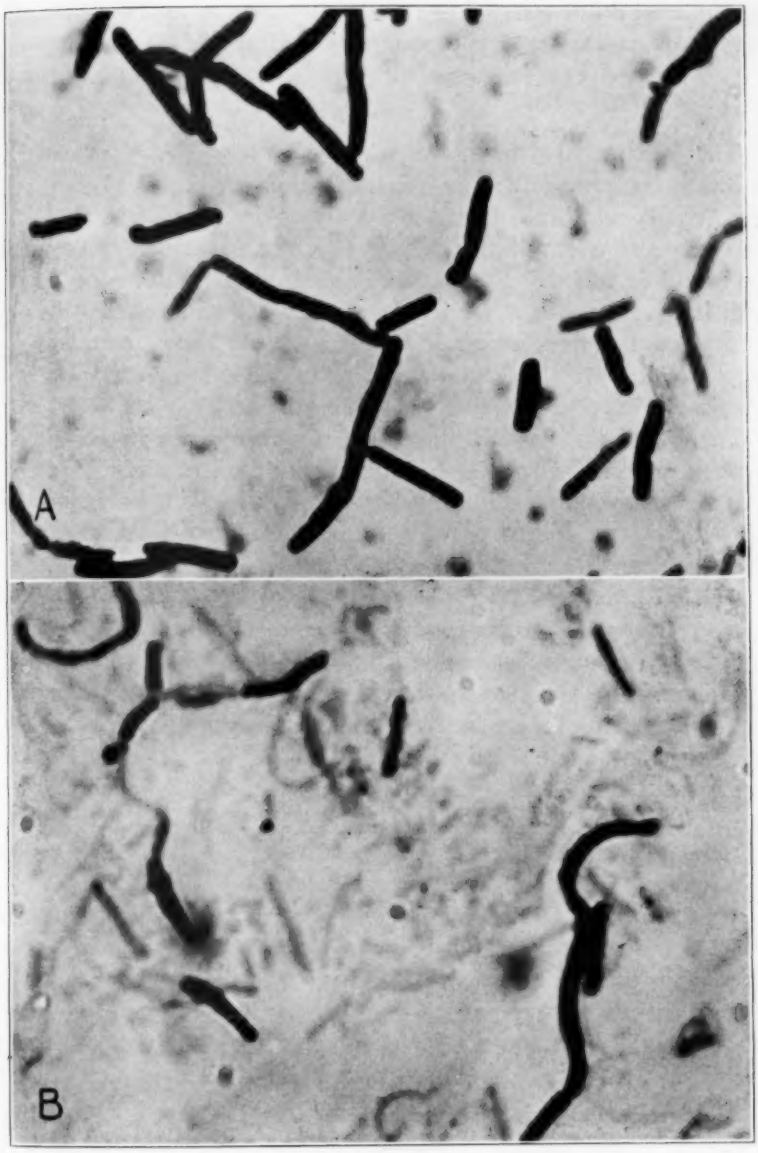

Fig. 6.—*A*, muscle organism in an eighteen hour surface colony in dextrose heart infusion agar under carbon dioxide. *B*, muscle organism from a colony three months old on 1 per cent dextrose, 3 per cent liver agar in anaerobic tube (note the spore in the lower right corner).

chloride would cause death in twenty-four hours. Similar filtrates of organisms from liver and muscle were diluted and tested, and even in large doses of full strength we could demonstrate no harmful results. Rabbits, guinea-pigs and dogs were also used to test the material, which at no time gave toxic reactions.

COMMENT

The data included in this paper may serve to clarify much of the confusion concerning the gas-forming bacilli. It occurs to us that the term "gas bacillus" has been too loosely applied, and that it has been too commonly assumed that any gas-forming anaerobe is the Welch bacillus. We feel that this is true in previous reports on the cause of death in liver autolysis. We have not attempted to determine the exact identity of the liver or muscle organism; we have, however, used accepted cultural methods and strict bacteriologic technic to place these organisms within their proper metabolic group.

The organisms isolated from liver differ from those found in muscle in many respects. Organisms in muscle require less anaerobiosis, they form less gas, and they differ morphologically as well as in their reaction to heat. However, both types of organisms are spore-bearing anaerobes, they are nonmotile, they cause rapid digestion of meat with a strong putrefactive odor, and from the standpoint of exotoxin formation they are nonpathogenic. Organisms from both liver and muscle must occupy an entirely different place within the genus Clostridium than does the Welch bacillus. Damon and Feirer [10] described a group of thermophilic anaerobes which compare more closely to the organism isolated from dog liver than any that have been described. The organisms that we have isolated from liver differ from these thermophilic anaerobes only slightly in morphology and sugar fermentation. Muscle organisms do not compare with this group.

We do not insist that at all times we have been working with absolutely pure cultures. Our organisms were separated with care by means of picking off colonies and not by the single cell technic. We realize also that the number of specimens studied falls short of a quantity that would guarantee these organisms to be present in the livers of all normal dogs; with this in mind we are continuing to add specimens to this number as we study the rôle of anaerobic bacteria in death due to autolytic peritonitis, a report of which is to follow.

In two instances aerobic organisms were found in cultures from the liver, but were discarded without further study. It may be of interest to note that one of these organisms formed an intense red pigment in veal infusion mediums. It was also noted that the anaerobes present

10. Damon, S. R., and Feirer, W. A.: Anaerobic Sporulating Thermophiles, J. Bact. **10**:37 (Jan.) 1925.

in the sixteen livers grew poorly in pure culture. The rapidity of growth and destruction of protein is markedly increased by symbiosis with Staphylococcus and B. coli.

As a result of studies so far made, we do not believe that toxic strains of C. welchii regularly inhabit liver or muscle of living dogs. We doubt the probability of its presence in tissues of a living dog. We agree that the livers of fetal dogs are sterile. The liver and muscle become the habitat of these organisms only after the first few months of life and after the ingestion of food. We attempt no explanation of their presence in the liver or in other tissue, but we do point out that they probably enter actively into the reduction of the body after death. Whether or not they enter actively into the process of disease remains to be determined.

CONCLUSIONS

1. Toxic strains of C. welchii were not found to be present in the livers of sixteen normal healthy dogs or in the muscles of six normal healthy dogs.

2. The livers of sixteen normal healthy dogs contained a strict anaerobic bacillus, thermophilic in its reaction to heat, a member of the genus Clostridium and of the metabolic group of nonsucrose-fermenting, putrefactive, gas-forming organisms.

3. The muscles of five normal healthy dogs contained a less strict anaerobic bacillus, not thermophilic in heat reaction, a member of the genus Clostridium and of the metabolic group of sucrose-fermenting, putrefactive, gas-forming organisms. A sample of muscle from one dog was sterile.

4. The organisms occupying the livers and muscles of the dogs studied do not produce an exotoxin. They are, in this respect, non-pathogenic.

5. These organisms are all large gram-positive bacilli. Their morphology and gas production easily confuse them with pathogenic forms.

6. On two occasions when large masses of liver were incubated, organisms were found which closely resembled C. welchii in morphology. They differ in sugar fermentation, form no exotoxin and were not pathogenic when injected in young broth cultures intramuscularly into guinea-pigs.

7. Livers of fetal dogs are uniformly sterile.

This work has been done under the supervision of Dr. W. D. Gatch. Assistance has been given to us by Dr. Thurman B. Rice of the department of bacteriology and pathology and by Mr. Fred A. Miller and M. Galen Boring of the biological department of the Eli Lilly Research Laboratories.

TUMORS OF THE PAROTID GLAND

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BALTIMORE

Whether considered from the clinical, pathologic or therapeutic standpoint, tumors of the parotid gland present problems difficult of solution. The benign neoplasms of this organ often show malignant tendencies in that they recur frequently after simple excision, whereas the malignant tumors often show benign features in that distant metastases rarely develop. Whether recurrence in a given case is a clinical feature of a benign process or a malignant feature of a type of carcinoma in which a tendency to widespread metastases is practically absent is not always easily decided. The composition of the majority of these new growths as seen through the microscope is likewise difficult of interpretation. Whether these tumors are truly mixed, with both connective tissue components and epithelial elements taking part in the neoplastic process, is by no means clear from a perusal of the literature. Authors differ in placing the responsibility for the new growth on the epithelium, the connective tissue, the myxoma or the cartilage found in these lesions, and the view that the entire process is endothelial is not without its adherents. From the standpoint of treatment, equally difficult decisions must be made. Since the continued growth of these tumors and manipulations for their removal both offer serious danger of damage to the adjacent facial nerve, the choice between surgical intervention and irradiation is often an extremely delicate one.

The many factors to be weighed in diagnosis, in pathologic interpretation and in treatment, as well as the fact that the occurrence of these tumors is by no means rare, lends importance to a thorough restudy of a large series of these cases.

The frequency of tumors of the parotid gland is indicated by previous publications on this subject, series of cases numbering over 50

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(Wood [1] and Wilson and Willis [2]) and over 90 (Kennon,[3] McFarland,[4] Benedict and Meigs [5]) having been reported from various clinics. The following study of tumors of the parotid gland recorded in the surgical pathologic laboratory of the Johns Hopkins Hospital covers a period extending from 1888 to 1931 and includes a total of 241 cases. In most of these cases the records are complete and include both history and pathologic material. It has been possible to maintain close contact with the majority of these patients (145) for varying periods of time, and many of them have been followed from operation to the time of writing or until death. Infectious processes localizing in and affecting the parotid gland have not been included in this study, which is restricted to the neoplasms of the gland.

CLINICAL FEATURES OF PAROTID TUMORS

In a group of 50,000 patients surgically treated there were 241 parotid tumors (exclusive of those that were definitely submaxillary, sublingual or lacrimal), a ratio of 1 tumor to 208 persons. Of the 241 tumors, 42, or 17.4 per cent, were considered malignant after a study was completed of all data on which classification could be based. Parotid tumors may occur at any age, and in the present series ages are recorded from 8 to 80 years. Pailler [6] reported a tumor in a girl of 11 months; McFarland,[4] a tumor in a child less than 1 year of age, and Wood,[1] a rapidly growing tumor in a child of 7 months. Although there is a fairly wide age distribution, the majority of these tumors appear in persons between the ages of 20 and 45 years, with the highest incidence in the third decade. If the cases reported by McFarland and those he collected from the literature are added to the series of Benedict and Meigs [5] as well as to the series cited here, there is a total of 676 cases, of which 455 occurred in persons between the ages of 20 and 45 (fig. 1). A larger percentage of malignant tumors than of

1. Wood, F. C.: The Mixed Tumors of the Salivary Glands, Ann. Surg. **39**:57 and 207, 1904.

2. Wilson, L. B., and Willis, B. C.: The So-Called Mixed Tumors of the Salivary Gland, Am. J. M. Sc. **143**:656, 1912.

3. Kennon, R.: Tumours of the Salivary Gland, Brit. J. Surg. **9**:76 (July) 1921; **10**:85 (April) 1922.

4. McFarland, J.: Ninety Tumors of the Parotid Region, Am. J. M. Sc. **172**:804 (Dec.) 1926.

5. Benedict, E. B., and Meigs, J. V.: Tumors of the Parotid Gland, Surg., Gynec. & Obst. **51**:626 (Nov.) 1930.

6. Pailler, B.: Des épithéliomes polymorphes de le parotide, Thèse de Paris, 1903.

benign tumors occurred in persons over the age of 45, although the highest number of malignant tumors occurred in the third decade.

The incidence of these tumors is found to be greater in the white race (80.1 per cent) than in the Negro race (19.9 per cent). One case of carcinoma of the parotid occurred in a Chinaman. The two sexes were about equally affected. The tumors occur with practically equal frequency on both sides of the face, as follows:

	Right	Left
McFarland reports	28	38
McFarland reports from other sources	114	135
	225, or 47.2%	251, or 52.8%
Present series	70, or 52.6%	63, or 47.4%

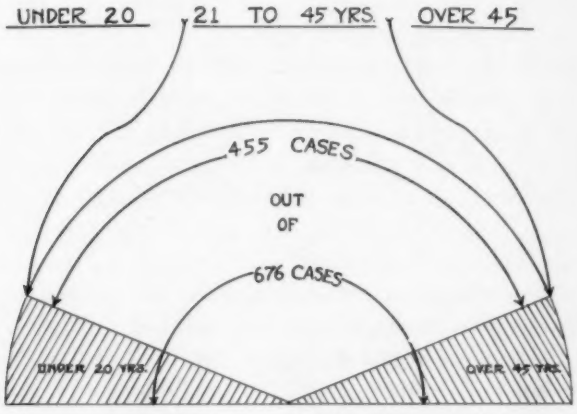

Fig. 1.—Chart showing age incidence of parotid tumors.

Concerning localization, the following statistics may be noted:

	Cases	Percentage
Angle of the jaw	64	48.1
Over the parotid gland	21	30.8
Submaxillary region	13	9.9
Mastoid region	8	6.0
Throat	7	5.2

The average duration of the benign mixed tumors of the parotid from the time a mass was first noticed to the time of operation was ninety-six months, or eight years. The average for the malignant form was fifty-one months, or slightly over four years. The symptoms in nearly one half of the cases of malignant tumors were of fifteen months' duration or less, whereas the duration of symptoms in only one eighth of the benign mixed tumors was within the same period. The shorter duration in the malignant form indicates definitely a more rapidly grow-

ing process. Such symptoms as pain, interference with hearing or sight and involvement of the seventh nerve occurred earlier in the malignant form and caused the patient to seek medical aid sooner than in the case of the benign tumor. This, as pointed out by McFarland,[4] is an aid in differential diagnosis between the benign and the malignant form.

Frequently a history was obtained of the presence of a nodule which was quiescent for as long as ten years, and which then manifested slow and progressive growth. In some cases this followed injury or infection, but most frequently no reason was found, and apparently neither trauma nor infection could be related definitely to the mixed tumors as a causative factor.

Delbet and Herrenschmidt[7] reported some cases following trauma. Kennon stated that a number of his patients gave a history of an injury

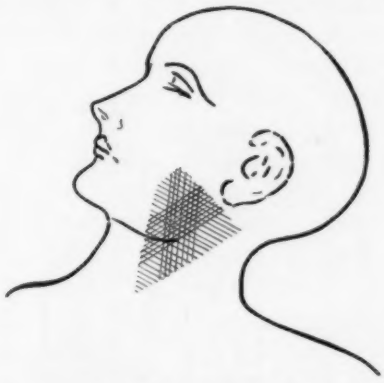

Fig. 2.—Chart showing the distribution of 241 parotid tumors.

to the area in which the tumor subsequently developed. In only 10 cases of the present series was there a history of trauma, and in but 14 a history of infection (mumps, influenza, sore throat or dental abscess) antecedent to tumor formation. It would thus appear that there is no definite evidence of any predisposing factors in the development of these tumors that can be obtained from the clinical history.

In the benign mixed tumors the most frequent symptom (fig. 3) was gradual growth with intervals of quiescence (even as long as ten years) usually followed by the slow and progressive enlargement so characteristic of these lesions. Rapid growth was rare, and when it occurred it was usually at the onset or just before operative intervention. Gradual growth occurred in 144 cases; rapid growth, in only 23.

Enlargement was rapid in 17 of the 42 malignant tumors, and in 7 the rate of growth varied a great deal during the course of the

7. Delbet and Herrenschmidt: Tumeur mixte de la parotide, Bull. Assoc. franç. p. l'étude du cancer **4**:41, 1910.

disease. In 17 cases in the malignant group, the mass was evidently adherent to some structure, either to the skin above or to the underlying tissue; in 10 early cases it was adherent to the skin alone. When there was an attachment to the structures below, the growth was always adherent to the skin. Such adherence is the most constant clinical sign of malignancy.

Local pain, rarely radiating to the scalp or to the upper half of the face, occurred in 37 of 151 benign lesions. The character of pain

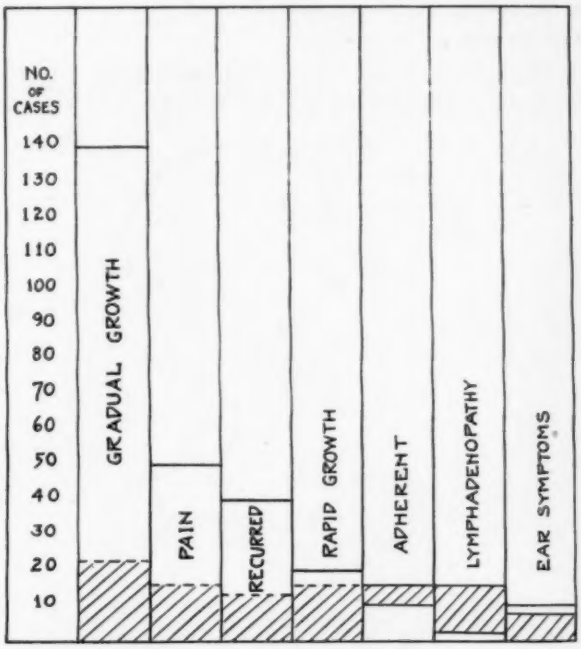

Fig. 3.—Chart showing the symptoms and findings in benign (white area) and malignant (crossed area) tumors of the parotid gland.

aids in the differentiation between the benign and the malignant form of parotid tumors. In 15 cases of malignant tumor there was pain of the radiating type. Although pain may occur in both the mixed and the malignant tumors, in practically all of the benign growths there is discomfort rather than pain, which is local rather than radiating.

In the entire series interference with chewing was noted three times, apparently caused by mechanical interference of the growth with the temporomandibular joint. Dysphagia was a rarer symptom, occurring but two times; in each case the tumor occurred in the pharynx, the explanation again probably resting on mechanical interference. Drainage of purulent material from the ear in otitis media, in association

with a tumor on the same side, was noted in 3 cases. Salivation was not observed in our series, though it has been described in the literature (Prengrueber [8]).

The benign tumors were of firm consistency, rubber-like, sharply circumscribed and not attached. The malignant tumors were usually more diffuse, more apt to be attached to the surrounding tissues and of a more variable consistency; they were at times harder and at times softer, but rarely of the same firmness as benign tumors. In 3 cases of the malignant group the tumor was noted to be rather soft in consistency and not at all circumscribed. In the other cases it was much firmer, and in a few cases it was quite discrete.

Enlargement of the cervical lymph nodes is another point of differentiation. In the malignant tumors this occurred in 13 of 42 cases, or in 30.9 per cent; whereas in the benign tumors it occurred in but 7 of 153 cases, or 4.5 per cent. The lymphatic involvement was unilateral in but 1 case of the malignant group and was bilateral in all the rest. It was confined to the cervical nodes in all the cases, with an exception in the benign group which was associated with a general enlargement of lymph nodes. In but 1 case was the swelling definitely proved to be caused by metastasis from the tumor. In others it was present when the patient presented himself for examination, but it could easily have been due to some infectious process, particularly about the upper respiratory tract. To support this view is the fact that in no case in this series was there other than a unilateral tumor, yet all cases of enlarged lymph glands save 1 were bilateral, and this case showed definite glandular enlargement after the onset of the tumor.[8a]

CLINICAL DISTINCTION BETWEEN BENIGN AND MALIGNANT TUMORS

Although the differentiation of benign from malignant tumors of the parotid gland is often an extremely difficult problem in the symptomatology and in the clinical examination, distinction between benign and malignant tumors can usually be made. Three of 4 benign tumors occur in the age period between 20 and 45 years, whereas 2 of 3 of the malignant tumors occur after 45 years and between the ages of 45 and 65. The duration of the benign tumors is twice that of the malignant, the former averaging eight years and the latter four years. Pain is mild and localized in the benign group, and is severe and radiating in the malignant group. The rate of growth is slow and gradual in one

8. Prengrueber, cited by Ewing.[29]

8a. In only four cases among the malignant tumors of this series were metastases to distant organs verified. While the impression clinically is that a fair percentage of parotid cancers metastasize to the regional lymph nodes, such metastases are seldom verified microscopically, and are rarer than is generally supposed.

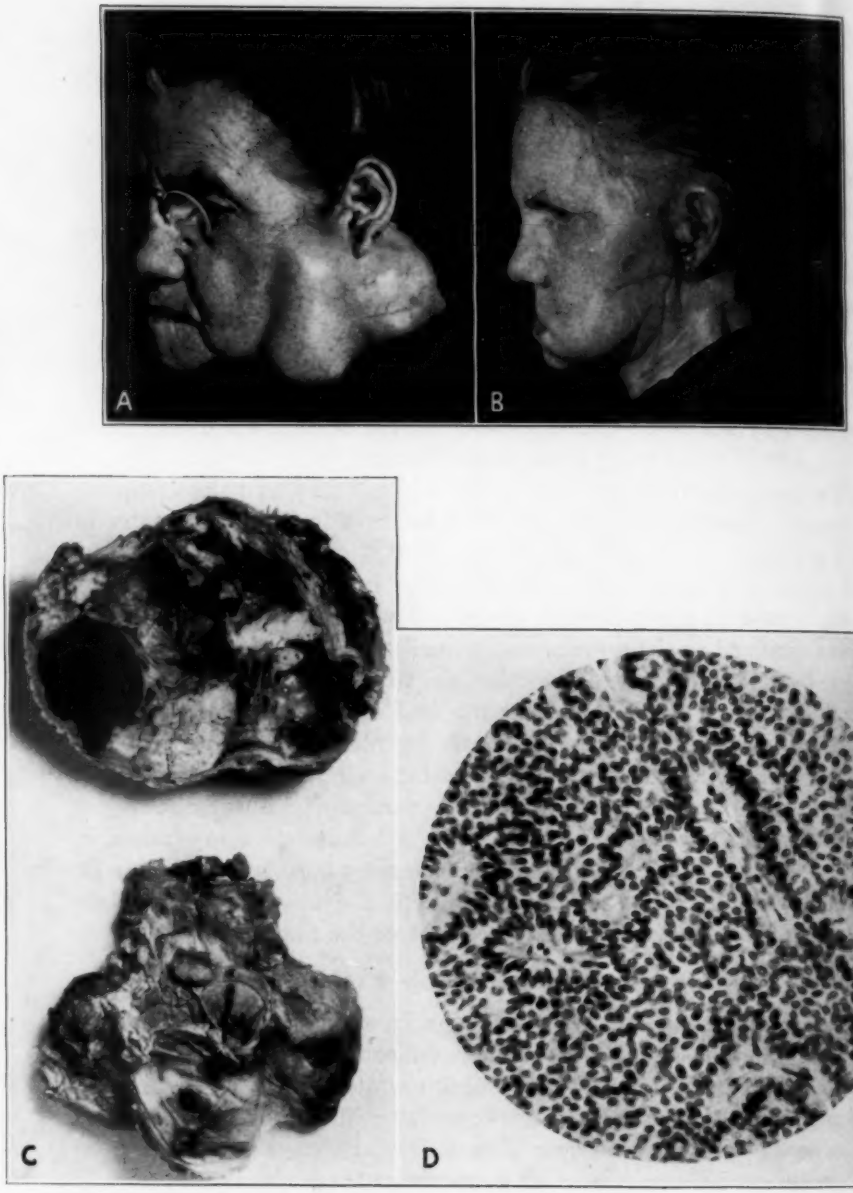

Fig. 4 (path. no. 21990).—Typical benign mixed tumor of the parotid gland. The patient was a white woman, aged 60, who had a tumor for twenty years at the angle of the left jaw. It grew gradually and progressively and became adherent below. There were no other symptoms. On Aug. 14, 1917, a complete excision of the tumor with the cautery was done. On Jan. 10, 1928, the patient died, ten and a half years after operation from other causes without evidence of recurrence. The pictures show:

A, side view emphasizing the lobulated character of the tumor.

B, postoperative result showing the scar and the drop of the lower part of the cheek. The facial nerve was severed in this case.

C, gross specimen. The upper illustration shows the cut surface; the lower, the capsule about the tumor. The cut surface is fibrillar and cystic. The outer surface shows the capsule enclosing the facial nerve.

D, photomicrograph showing the adenomatous character of the more cellular areas.

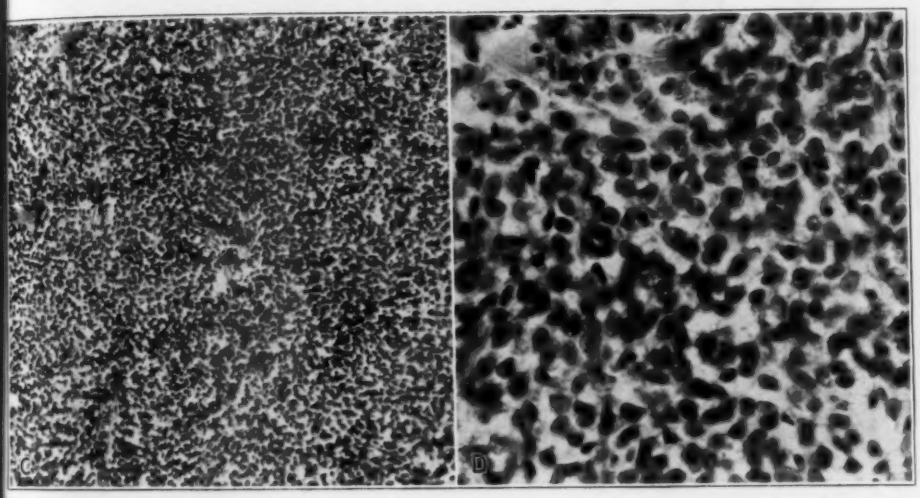

Fig. 5 (path. no. 26733).—Carcinoma of the parotid gland metastasizing to the cervical nodes and to the abdomen. Death occurred within two years. The patient was a white woman, 71 years old. She had a tumor for four years on the right side of the face at the angle of the jaw. It was about 2.5 cm. in diameter when first observed, but gradually and progressively grew and became adherent to the surrounding tissues and ulcerated on the crests. The patient lost much weight, and her cervical lymph nodes increased in size. The tumor was excised on Sept. 14, 1920; following operation she was better for a while; then there occurred bilateral metastases above the sternocleidomastoid muscles and later a mass in the abdomen. She died on Feb. 15, 1922, presumably from metastasis. The illustrations show:

A, patient before operation with a large ulcerating mass.

B, patient after operation with recurrence in the left cervical region.

C, low power photomicrograph showing diffuse grade III cancer.

D, high power photomicrograph showing malignant cuboidal cells.

group and more rapid in the other, the most rapid rate of growth being present in the more malignant lesions. On examination, a benign tumor of the parotid gland shows an encapsulated, firm, rubbery and nodular growth without enlargement of the regional lymph nodes. The malignant growth shows a more diffuse, adherent swelling which is either harder or softer than the benign lesion and which may be associated with an enlargement of the regional lymph nodes. These malignant tumors rarely ulcerate and fungate through the skin (figs. 4 and 5).

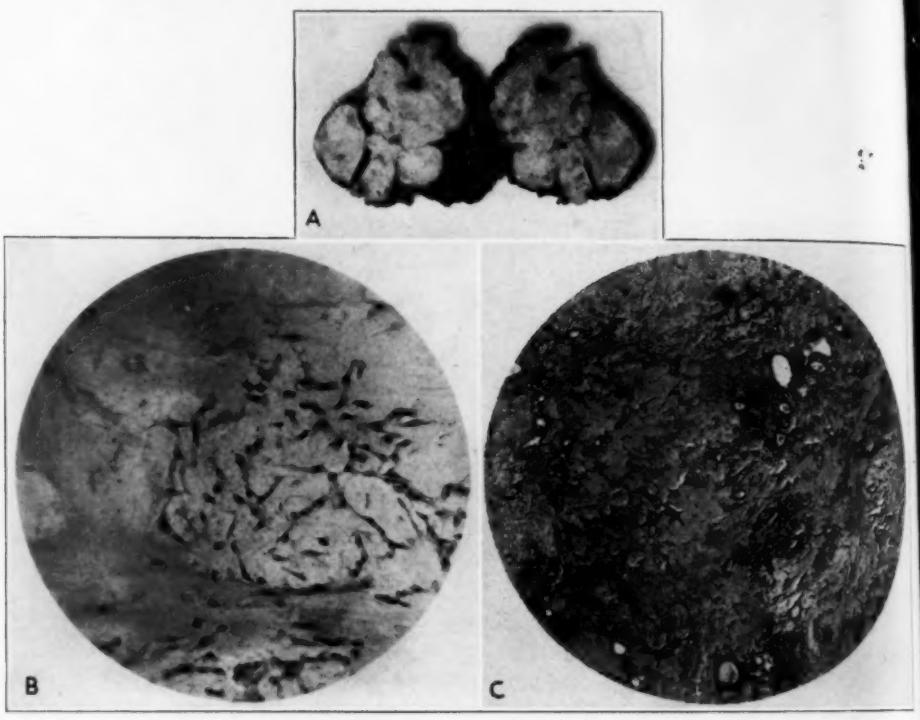

Fig. 6 (path. no. 23480).—Benign mixed tumor of the parotid with scanty and inconspicuous epithelial elements. The patient was a white woman, aged 31, who had a tumor behind the ear for ten years. It grew slowly and progressively, and there was local pain from the onset. A complete excision of the tumor was done on July 23, 1918. In 1919, the patient was well with no recurrence.

A, gross specimen showing the hyaline and cartilage-like areas visible on the cut surface.

B, photomicrograph showing the cartilaginous and precartilaginous stroma practically devoid of epithelial elements.

C, photomicrograph showing epithelial elements invading myxomatous areas.

PATHOLOGIC DISTINCTION BETWEEN BENIGN AND MALIGNANT TUMORS

In some cases in which the patient is middle aged with symptoms of several years' duration and the tumor is firm, but not definitely circumscribed, the distinction between benign mixed tumor and carcinoma of

the parotid cannot be made clinically. In other cases in the same age group with a similar duration of symptoms, the primary tumor may have been unsuccessfully excised elsewhere, and the recurrent growth may be even more difficult to diagnose. In such cases, particularly when tissue is already available for microscopic examination in a recurrent tumor, the pathologic changes may aid making the distinction.

The microscopic study shows a variation in cell structure with points of distinction between the more definitely benign groups, those with the greatest tendency to recur and those which terminate in death. The

Fig. 7 (path. no. 35501).—The patient was a white woman, aged 31, with a tumor of ten years' duration at the angle of the left jaw. Complete excision was performed in May, 1924, including a margin of normal parotid gland. A partial facial paralysis resulted. The photomicrograph shows the epithelial elements scattered among a large amount of fibrous and fibromyxomatous tissue in which many cystic spaces have formed.

most benign group has an adenomatous arrangement with a large amount of stroma in which myxomatous connective tissue and cartilage may be conspicuous features. The epithelial cells may be cuboidal, columnar or oval but are usually spindle-shaped and compressed by the abundant amount of stroma or matrix. These growths are referred to as mixed tumors of the parotid gland. Such typical mixed tumors are usually one of two microscopic types. In the first microscopic type, compressed basal cells arranged in thin strands pervade a lobulated and

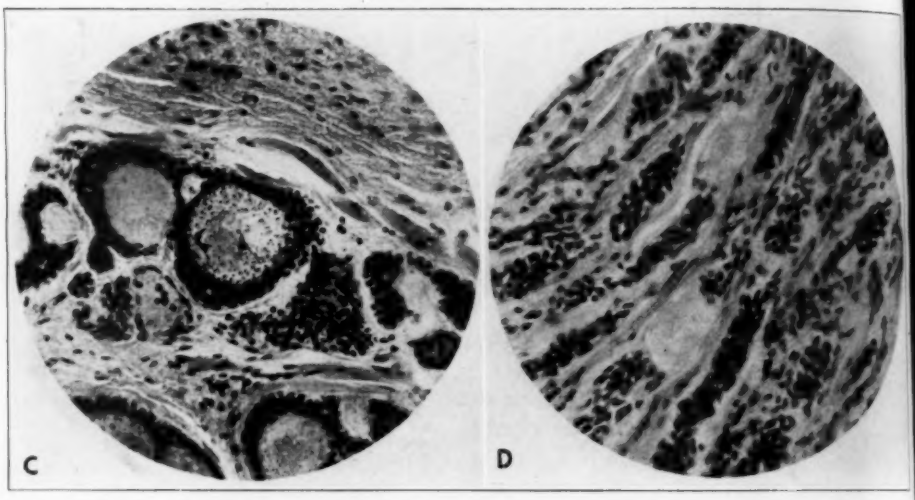

Fig. 8 (path. no. 23146).—Recurrent mixed tumor of the parotid. The patient was a white woman, aged 40, who had a tumor for three years which began just below the posterior zygoma and spread to the temporal region. It grew slowly. On May 8, 1918, it was excised piecemeal with the knife and the capsule broken. The tumor recurred a few months later. One year after this first operation radium treatments were begun and continued for eight months without improvement. In March, 1920, piecemeal excision with the cautery was done. The facial nerve was sacrificed. The cauterizations were done at repeated sittings. One year later, July 9, 1921, the patient was examined and found free from recurrence. The illustrations show:

A, patient after the first operation.

B, patient after cauterization for recurrence.

C, high power photomicrograph from the recurrent specimen showing nests of basal cells invading the stroma. There is a definite adenocystic arrangement.

D, high power photomicrograph from the recurrent specimen showing the compressed basal cells intermingled with myxomatous fibrous tissue. In *C* and *D*, it can be seen that the tumor approaches adenocystic basal cell carcinoma in structure.

myxomatous matrix (fig. 6*A* and *B*). In the second microscopic type, the epithelial cell varies from a basal to a cuboidal or even to a squamous cell, and the stroma with numerous cystic spaces shows similar variations including hyalinized connective tissue, myxoma or cartilage (fig. 7). Microscopically, the most reliable index to the benign nature of these mixed tumors is the character of the stroma. The slower the rate of growth the larger is the amount of stroma and the more often is cartilage found.

In the recurrent tumor, areas of diffuse proliferation may be seen. The stroma is more predominantly fibrous than myxomatous, and the epithelial cells are more uniformly of the basal cell type. These cell

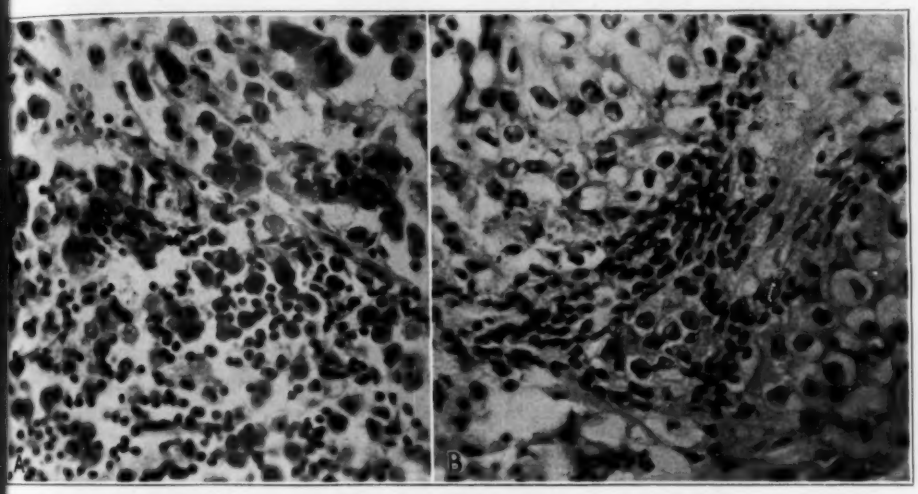

Fig. 9 (path. no. 9120).—Metastasizing carcinoma of the parotid gland. The patient was a white man, aged 45, with a gradual growth in the right parotid region of three and one-half years' duration. Enlargement of the lymph nodes appeared two months before death. Despite irradiation and tracheotomy, death occurred within less than four years after the initial operation.

A, diffuse invasion of the parotid gland by malignant epithelial cells.

B, structure of the tumor in a lymph node. Nests of large epithelial cells are seen.

groups may be arranged in an apparently adenocystic formation or in islands invading the stroma rather than in strands as seen in the mixed tumors (fig. 8). In the recurrent cases the microscopic picture overlaps that of so-called benign mixed tumors on the one hand and that of carcinomas on the other, since basal cell proliferation may predominate over the components of any of the three groups. Many of these recurrent tumors are basal cell carcinomas without a tendency to metastasize. Some of them are benign mixed tumors of the parotid with basal cell features which become more prominent after the first recurrence.

These tumors with basal cell features must be distinguished from a small group of malignant tumors of the parotid which are not related to the mixed or basal cell type but arise about the small ducts of the parotid and may produce diffuse islands of cuboidal cells or metastasize as cuboidal cell cancer (fig. 9). Another small group of malignant tumors composed of small spindle and round cells (fig. 5), described by Chevassu [9] as atypical carcinoma, approaches the basal cell cancer in structure. This is the type incorrectly described by Kuster,[10] Nasse,[11] Degen [12] and Schridde [13] as round cell sarcoma. These rare variants of cancer of the parotid are best referred to as atypical carcinoma after Chevassu.

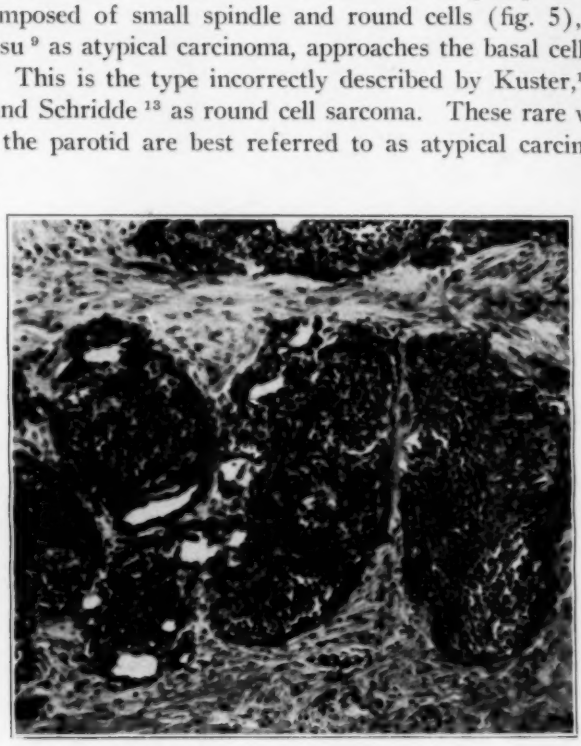

Fig. 10 (path. no. 36754).—Recurrent basal cell cancer. The tumor, in a white woman, aged 42, was present nearly four years. It recurred twice and invaded the lymph nodes. Despite the last complete excision performed in June, 1925, there was recurrence with failing health in May, 1931. The photomicrograph of the basal cell cancer shows characteristic epithelial lobules with invasion of the fibrous stroma.

9. Chevassu, Maurice: Tumeurs de la gland sous-maxillaire, Rev. de chir. **41**:145, 1910.

10. Kuster, F.: Arch. f. klin. Chir. **12**:596, 1870.

11. Nasse, D.: Die Geschwülste der Speicheldrüsen und verwandte Tumorendes Kopfes, Arch. f. klin. Chir. **44**:233, 1892.

12. Degen, W.: Ein doppelseitiges Sarkom der Parotis, Inaug, Dissert., Freiburg, 1900.

13. Schridde, H.: Ein Rundzellensarkom der Parotis, Beitr. z. path. Anat. u. z. allg. Path. **34**:136, 1903.

When the patient is over 45 years of age, and when the tumor is adherent and rapidly growing, a neoplasm of the parotid may be expected to show basal cell features and to have a tendency to recur. A definite percentage of this group are true basal cell cancers (fig. 10). Only in rare instances will there be an atypical carcinoma (Chevassu) which has a tendency to metastasize. The firm nodular growths occurring in persons under the age of 45 with a longer duration of symptoms and a slower rate of growth usually will prove on microscopic examination to have mixed features with a large amount of myxomatous stroma and epithelial components containing benign cells arranged in thin strands or dilated acini. They will have less tendency to recur after treatment.

Thus there are pathologic factors leading to recurrence after treatment of tumors of the parotid. The recurrent tumor is most often a basal cell carcinoma or a benign mixed tumor with basal cell features. The microscopic distinction between the two is associated with clinical points of differentiation, as has been pointed out.

THE NATURE OF MIXED TUMORS

Difficulties in the histogenesis of parotid tumors have hinged about both the epithelial and the connective tissue components of the neoplasm. Although Kaufmann and Volkmann tried to derive these lesions from endothelium, it is now generally conceded that the more cellular areas are epithelial. The more difficult problem has been to account for the myxomatous and cartilaginous features found in the stroma. Krompecher,[14] Clementz [15] and others have thought that metaplasia or mucoid regression might account for the cartilaginous material as a product of the epithelial cells in the tumor.

These tumors were first described by Kaltschmied [16] in 1752. They were regarded as epithelial by Virchow [17] even though he pointed out the probable derivation of cartilage from connective tissue by metaplasia. Cohnheim [18] particularly was an adherent of the epithelial theory of the origin of these tumors.

This opinion persisted until Kaufmann [19] attempted to prove a relationship to endothelial structures on the basis of peritheliomatous

14. Krompecher, E.: Zur Histogenese und Morphologie der Mischageschwülste der Haut, sowie der Speichel- und Schleimdrüsen, Beitr. z. path. Anat. u. z. allg. Path. **44**:51, 1908.

15. Clementz, H.: Ueber das Schleimgewebe in Parotisgeschwülsten, Inaug. Dissert., Bonn, 1882.

16. Kaltschmied, C. F.: Tumore scirrhoso trium cum quadrante librarum glandulae parotids extirpato, Vienna, lit. Tennemannianis, 1752.

17. Virchow: Die krankhaften Geschwülste, Berlin, A. Hirschwald, 1863-1867.

18. Cohnheim: Virchows Arch. f. path. Anat. **68**:547, 1876.

19. Kaufmann, C.: Das Parotis-Sarkom pathologisch-anatomisch und klinisch bearbeitet, Arch. f. klin. Chir. **26**:672, 1881.

and sarcomatous-like features. Then, Wartmann [20] in 1879, because of the polyhedral cells so frequent in the histologic structure of these tumors, maintained that they were derived from lymphatic endothelium. There appeared to be some truth in this contention, for these cells are small and polyhedral, and assume a flat or spindle form under pressure. Often they are adherent to the supporting connective tissue and appear to merge with it in a manner certainly suggesting an endothelial nature.

These observations so influenced Volkmann [21] that in 1895 he made a comprehensive study of the subject. He pointed out to what degree these tumors may simulate endothelial structures, and turned the tide of thought in the direction of the endothelial theory. For some time case reports were published under the heading of "Endothelioma of the Parotid."

The swing of opinion back to the epithelial theory of origin started in 1899 with Hinsberg,[22] who was supported by Ribbert [23] and later by Borrmann [24] in 1901. These men, by careful investigation and study of various cases, so adversely criticized the endothelial theory that there was a reversion of thought to the earlier views of Cohnheim.

In France, opinion had always been in favor of the epithelial origin, and though there was some dissension (Curtis and Phocas [25]) the theory was earnestly upheld by Collet [26] in 1896, Pitancé [27] in 1897, and Cunéo and Veau [28] in 1900.

In 1912, Weishaupt [29] and later Moral [30] agreed on the idea that the ramus of the mandible might furnish the peculiar embryonal material

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20. Wartmann: Untersuchungen über der Enchondrom, Inaug. Dissert., Strassburg, 1880.

21. Volkmann, R.: Ueber endotheliale Geschwülste, zugleich ein Beitrag zu den Speicheldrüsen-und Gaumentumoren, Deutsche Ztschr. f. Chir. **41**:1, 1895.

22. Hinsberg, V.: Beiträge zur Entwicklungsgeschichte und Natur der Mundspeicheldrüsengeschwülste, Deutsche Ztschr. f. Chir. **51**:281, 1899.

23. Ribbert, M. W. H.: Geschwulstlehre für Aerzte und Studierende, Bonn, F. Cohn, 1904, p. 385.

24. Borrmann: Virchows Arch. f. path. Anat. **157**:297, 1899.

25. Curtis and Phocas: Contribution à l'étude des tumeurs mixtes de la parotide, Arch. prov. de méd. **1**:7, 1899.

26. Collet, André: Des tumeurs mixtes des glandes salivaires des levres, Thèse de Paris, 1895, no. 277.

27. Pitancé, J.-B.: Etude sur les tumeurs mixtes du voile du palais, Thèse de Paris, 1897, no. 610.

28. Cunéo and Veau: Sur l'origine branchiale des tumeurs mixtes cervico-faciales: branchiomes cervico-faciaux, Cong. internat. de méd., chir., Paris, 1900, vol. 10, p. 278.

29. Weishaupt, Elizabeth: Ein embryonaler Seitenganz des Ductus parotideus und seine Beziehungen zu einigen tumoren der parotis, Arch. f. klin. Chir. **100**:542, 1912.

30. Moral, Hans: Ueber die ersten Entwicklungsstadien der Glandula parotis, Anat. Hefte **47**:383, 1913.

often included in these tumors. This might explain the beginning of the process but certainly not the very complex differentiation that later occurs. As early as 1882, Clementz [15] expressed the opinion that cartilage in mixed tumors of the parotid might be formed from epithelial cells. In 1888, Carrière [31] studied ramifying cells in the cartilage of

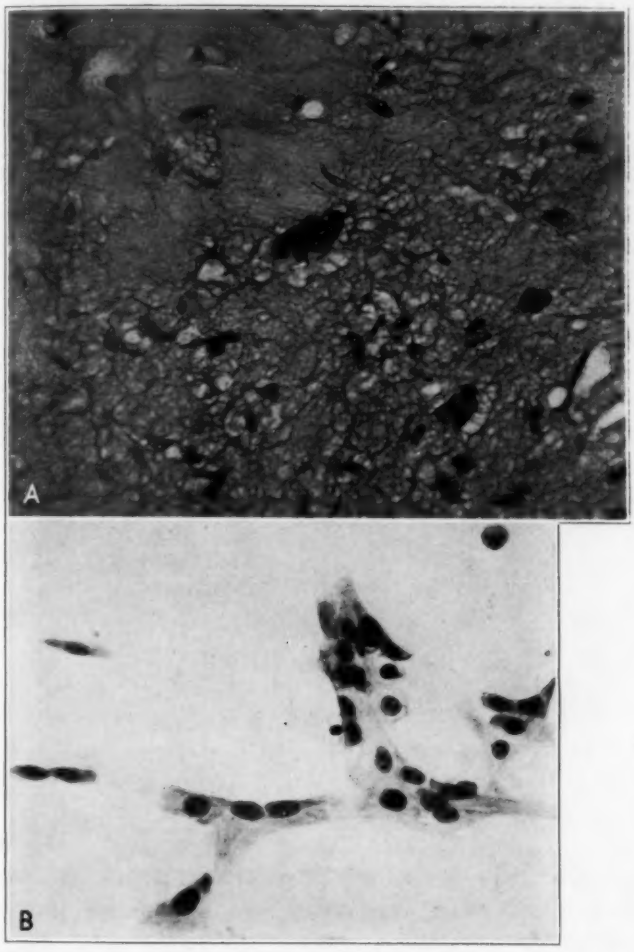

Fig. 11 (path. no. 50579).—Comparative histology of benign mixed tumor in section and in tissue culture. The patient was a white woman, aged 35, with a small hard tumor beneath the right ear, present for ten years. On Nov. 11, 1931, a complete excision was performed.

A, section showing spindle and epithelial cells lying loose in the stroma.

B, tissue culture showing spindle and epithelial cells in the culture medium.

31. Carrière: Note sur le développement des cellules ramifiées du cartilage des céphalopodes et de leurs rapports avec certains éléments des chondrome, Compt. rend. Soc. de biol. **5**:577, 1888.

cephalopods and their relation to the chondrotomes. Ehrich,[32] in 1906, maintained that the cartilage resulted from a condensation and the chemical transformation of the epithelial cells which had undergone a mucoid degeneration. Alezais and Bricker[33] also upheld these views and attempted to correlate them with the work of Carrière, in that they believed that similar ramifying cells, of the type occurring in the cephalopods, occurred in tumors of the parotid.

A restudy of the microscopic material of the cases in the present series and tissue cultures from human tumors of the mixed type grown

Fig. 12.—Human embryo 4501 of 18 mm. Anlage of the parotid gland showing the continuity of the epithelial elements with the lining of the buccal cavity: *A*, anlage of the parotid gland; *B*, Meckel's cartilage, and *C*, buccal cavity.

in vitro showed that the actively proliferating tumor element is an elongated basal cell which transforms into a more cuboidal or more columnar type (fig. 11). This is borne out by the embryology of the salivary glands, which in their early stages are outpouchings of the buccal epithelium (fig. 12). It is apparently the outlying cords or strands of this glandular epithelium invading the connective tissue of

32. Ehrich: Zur Kenntnis der Speicheldrüsentumoren, Beitr. z. klin. Chir. **51**:368, 1906.

33. Alezais and Bricker: Le cartilage a cellules ramifills des tumeurs parotidiennes, Compt. rend. Soc. de biol. **64**:380, 1908.

the capsule that is responsible for the beginning of the neoplastic process (fig. 14 *B*).

The tendency for the connective tissue components and their derivatives, myxoma and cartilage, to assume a prominent place in the microscopic composition of the tumor may be accounted for on embryologic grounds. Unlike the submaxillary glands, where such mixed tumors are relatively rare, the parotid from the earliest stages of its development lacks a specialized fibrous capsule (fig. 13). Instead, the epithelial cells diffusely invade the surrounding mesenchymal elements

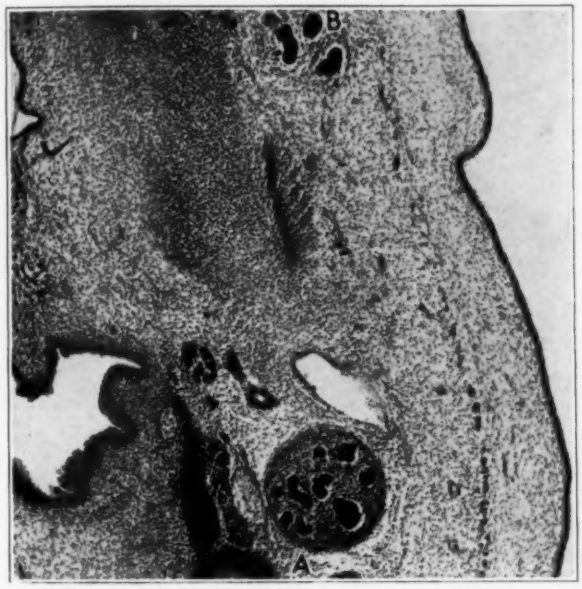

Fig. 13.—Human embryo 5725 of 23 mm. Photomicrograph from the region of the jaws. The section shows the contrast between the early stages of development of the submaxillary gland *A* and the parotid gland *B*. Note the lack of encapsulation of the epithelial buds of the parotid and the definite formation of a capsule about the submaxillary gland.

in the region of Meckel's cartilage. From the first the parenchyma of the gland is thus closely associated with the precartilaginous structures of the mandible. This lack of definite encapsulation during development was emphasized by Löwenkron [34] and was noted by

34. Löwenkron, Hans: Ueber Entwicklung des Bindegewebes der grossen Mundspeicheldrüsen (bei menschlichen Embryonen), Ztschr. f. Anat. u. Entwcklngsgesch. **93**:370, 1930.

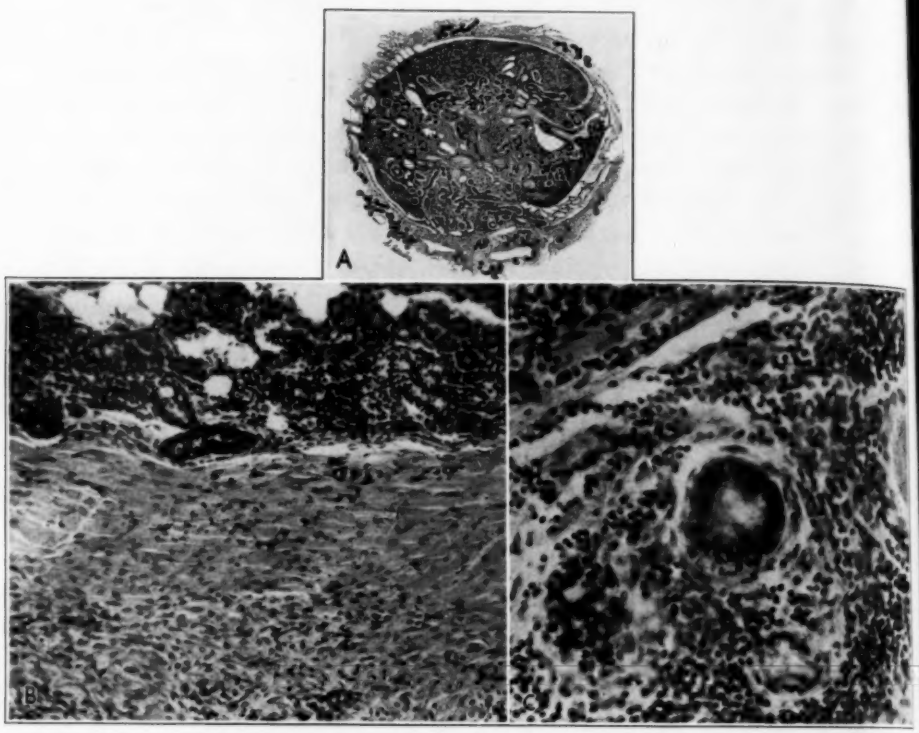

Fig. 14.—*A*, invasion of the normal lymph node by epithelial buds of the parotid gland in a human fetus of 21 cm. (After Neisse: Anat. Hefte **10**:287, 1898.)

B, photomicrograph of the margin of a normal lobule of the parotid gland in an adult showing the undeveloped buds of parotid epithelium at the capsule of the gland. Apparently these undeveloped buds of parotid tissue penetrate the surrounding capsule of connecting tissue, and the lymph nodes in the immediate region give rise to tumors of the parotid of the mixed type.

C, high power photomicrograph of a lymph node in the capsule shown in *B*. The illustration shows distinctly the invasion of the normal lymph node in an adult by the outlying buds of parotid epithelium, corroborating the findings of Neisse.

Delemare, Poirier and Cunéo.[35] Neisse [36] even observed invasion of the embryonic lymph nodes by normal epithelium of the parotid (fig. 14*A*). This tendency for the outlying acini of the gland to invade surrounding structures is seen in normal anatomic specimens that have been subjected to microscopic study (fig. 14*B* and *C*). During the process of

35. Delamare, Poirier and Cunéo: Anatomy of the Lymphatics, translated by C. H. Leaf, Chicago, W. T. Keener & Co., 1904, p. 250, fig. 94.

36. Neisse, R.: Ueber den Einschluss von Parotisläppchen in Lymphknoten, Anat. Hefte **10**:287, 1898.

tumor proliferation it is the outlying glandular elements (which normally retain the greatest growth potentialities) that are most active. Their invasion of the surrounding connective tissue apparently stimulates this precartilaginous substance to react and to proliferate. The result is a composite tumor of both epithelium and connective tissue.

PATHOLOGY OF CARCINOMAS OF THE PAROTID

The majority of the malignant tumors of the parotid are of the basal cell type (fig. 10). Although these tumors are usually adherent to the overlying structures, the skin is rarely ulcerated and there is no evidence to prove that these cancers arise from the basal cells of the epidermis. The carcinomas develop rapidly and are apparently circumscribed at first, but they soon become attached to adjacent structures, invade the gland, and finally involve the regional lymph nodes. Infiltration of the adjacent tissues is not infrequent in the malignant tumors, and occasionally the axillary and mediastinal lymph nodes are involved. Distant metastases are, however, extremely rare. Nasse observed local and general metastases that in 1 case extended to the bones. Although it was assumed on the evidence of gross pathologic examination that cartilage was present in 3 cases in the group of carcinomas, cartilage could not be found on microscopic examination. The fibrous constituents present are usually much overshadowed by the epithelial proliferation.

The microscopic structure may be that of an adenocarcinoma with cells of the columnar or basal form, but more often it assumes adenocystic basal cell features. This tendency for the undifferentiated tumors of the parotid to approach basal cell cancer in type is to be expected, since it is the basal cell layer of the primitive buccal epithelium from which the salivary glands are derived. The same tendencies for tumors arising in the appendages of buccal epithelium to give rise to adenocystic basal cell carcinoma is seen in adamantinomas derived from the epithelium of the gums and in aberrant mixed tumors in the mucous membrane about the cheeks and the palate. Carcinomas of this basal cell type frequently recur and extend locally, but rarely metastasize. It is usually the atypical carcinomas which give rise to widespread metastases, as illustrated in the case of L. S., a white man, aged 45 (fig. 9).

Anatomic Diagnosis.—The anatomic diagnosis was probable mixed tumor of the right parotid gland with malignant change. There was extension to the tissues of the neck and the axilla with metastases to the left axillary lymph glands, the right thoracic wall and the skin over the right side of the chest. Other findings were an x-ray burn on the right side of the chest, edema of the right arm, edema of the uvula and the larynx, a tracheotomy wound, aspiration pneumonia, edema of the scrotum and old syphilitic scars of the liver.

37. Footnote 37 has been deleted by the authors.

Clinical History.—The patient had mumps in early childhood, since which a lump had persisted in the right parotid region. In December, 1925, the swelling began to increase in size, and irradiation was tried without success. An emergency tracheotomy had to be performed owing to acute dyspnea and edema of face and of the right arm.

Physical Examination.—The temperature was 101.6 F.; the pulse rate, 120, and the respiratory rate, 30. There was an induration of the skin of the face and chest with small red nodules. The patient at first improved; then there was a recurrence of edema and dyspnea over a three day period. He was kept under the influence of morphine for two days, and died with a terminal rise of temperature to 108 F. His urine, Wassermann reaction and blood culture were negative. Biopsy showed a chronic inflammation and cells suggesting malignancy.

Autopsy.—A huge, firm mass was found in the region of the right parotid. The mass seemed to fade indefinitely into the indurated tissues of the neck. The skin of the neck was thickened, edematous and bluish red. The circumference of the neck was greatly increased and felt quite hard across the front and around the side beyond each ear. The tissues about the tracheotomy wound were thick and edematous with numerous firm white nodules in the skin over the entire left side of the chest down almost to the costal margin, which did not seem to extend beyond the midline. The tissue in the right axilla was very dense, and the right arm was swollen. An x-ray burn with large blisters on the left side in the axillary line was noted. When the soft tissue was stripped from the ribs, the muscles of the entire right side of the chest contained patches of firm white tissue similar to that of the skin. The mass in the parotid region was removed and found to be firm and rather hard with an indefinable outline. When the mass was removed, it was noted that the tumor tissue extended around the neck as far as could be explored, about 8 cm. behind the right ear. On the right side of the neck the muscles were infiltrated by the same dense white tissue that was found in the left axillary glands. The thyroid gland was surrounded by tumor tissue and on section showed firm, pale areas due to an infiltration of the new growth.

Microscopic Examination.—Sections from the skin, larynx, lymph nodes and parotid all showed the same type of cellular neoplasm. The predominant cell was round or cuboidal with a single or double large hyperchromatic nucleus (fig. 9). Small spindle cells and many lymphocytes accompanied the epithelial elements, which were arranged in partial acini or small islands. The microscopic diagnosis was cuboidal carcinoma of the parotid, or so-called atypical carcinoma.

DIFFERENTIAL DIAGNOSIS

In addition to the difficulty of distinguishing between benign and malignant tumors of the parotid gland, there is also the problem of differentiating these neoplasms from swellings in the parotid region caused by other conditions. In the differential diagnosis, the following conditions must be borne in mind: epidemic or infectious parotitis, benign or malignant lymphadenopathy, salivary calculus, Mikulicz' syndrome, actinomycosis, tumors of the jaw and antrum and peritonsillar and buccal abscess.

Epidemic Parotitis (Mumps) or Infectious Parotitis.—These conditions should cause little difficulty in diagnosis. Both are accompanied by an acute onset with fever, rather than by the gradual course char-

acteristic of parotid tumors. Mumps is distinguished by the bilateral involvement, the acute pain and the history of an epidemic in the neighborhood. Infectious parotitis is usually found in surgical cases in which the proper quantity of fluids has not been given.

Lymphadenopathy.—The occipital nodes and posterior auricular nodes may become enlarged as a result of leukemia, Hodgkin's disease, lymphosarcoma, syphilis, tuberculosis or acute infection, but in these cases there is an obvious enlargement of the other cervical glands at the same time.

Hodgkin's disease or lymphosarcoma may begin with marked swelling in only one group of nodes on one side of the neck. The swelling is, however, more rapid than in a parotid tumor and spreads more rapidly to lymph nodes elsewhere in the body. Palpation of the spleen and liver, a roentgenogram of the chest to determine whether or not there is a mediastinal tumor and a blood count to determine the possible presence of lymphoid leukemia are important procedures in making the differential diagnosis. The early response of malignant lymphoid tumors to high voltage roentgen therapy is diagnostic.

Salivary Calculus.—Salivary calculus occasionally may be present in the parotid duct, although it is more frequently found in the duct of the submaxillary gland. In the early stages it gives rise to sudden intermittent swelling of the affected gland when stimulus from food causes active secretion. If the process is of long standing, the gland may become permanently distended. Diagnosis may be determined by palpation, probing or roentgen examination.

Mikulicz' Syndrome.—This condition is characterized by chronic bilateral swelling of the parotid, and of the submaxillary, sublingual and usually the lacrimal glands. Sometimes there are associated splenomegaly and lymphadenopathy as well as changes in the blood picture. The syndrome is associated with lymphadenoma, lymphatic leukemia or chronic infection.

Actinomycosis.—This condition is uncommon and has occurred primarily in the parotid only fifteen times (in the literature). In other instances involvement of the parotid has been secondary. At first there is a hard, brawny induration of the skin and subcutaneous tissues, and later there are suppuration and frequently a granular exudation. Diagnosis is confirmed by the finding of the sulphur-like granules in which one can stain the mycelium; in the secondary form diagnosis is further facilitated by the presence of other areas of infection. Suppuration and ulceration found in actinomycosis are rare in parotid tumors.

Tumors of the Jaw and Antrum.—Tumors bulging the antrum or arising in the jawbone may be distinguished by palpation from neoplasms of the parotid because of their continuity with the bones of the face.

When this is not possible, an x-ray film depicting the osseous involvement will aid in making the distinction.

Peritonsillar and Buccal Abscess.—In peritonsillar abscess there is generally an antecedent history of systemic reaction such as is evidenced by fever, chills and aching. In addition, there are present pain and difficulty in deglutition, a fluctuant mass, which is generally soft, located in the peritonsillar area, and also leukocytosis. Pus may be obtained from such a mass by incision, and if early surgical procedure is not resorted to, spontaneous rupture is likely to occur.

In a case of buccal abscess there is generally a systemic reaction, and the patient often suffers from fever and chills complicated frequently by aching of the bones. On examination the area in question is found to be soft and fluctuant. Relief from symptoms rapidly follows incision and drainage.

TREATMENT

These tumors often resist even the most radical treatment and frequently recur, sometimes with a fatal result, in spite of the most careful therapeutic measures. There have been four methods in common use by which these tumors have been treated. Although the tables indicating this and the results are complete and speak for themselves, there are a few points that deserve discussion. The methods of treatment (fig. 15 and tables 1 and 2) used are:

1. Curettage
2. Enucleation
   (*a*) With resulting damage to the capsule [38]
   (*b*) Without damage to the capsule
3. Complete excision
   (*a*) Tumor and healthy tissue surrounding capsule
   (*b*) Use of cautery to excise
   (*c*) Phenolization or use of alcohol in tumor bed
4. Irradiation by radium or roentgen rays.

In 7 cases the tumor was removed in fragmented form by curettage with contamination of the tumor bed by tumor cells. Recurrence took place in all cases in which this method of treatment was used. This danger is apparently not obviated by doing a thorough curettage aided by Paquelin cautery, phenol and alcohol or zinc chloride (50 per cent), for even in 3 patients treated in this fashion there were recurrences.

Another unsatisfactory method and one by which many of these tumors have been removed because of fear of injury to the seventh nerve is that of enucleation by blunt dissection. This is a temptation

38. The capsule referred to is macroscopic and not microscopic.

to even the most experienced of operators. It is, however, rarely achieved without some damage to the capsule, microscopic or macroscopic. This allows tumor cells to escape and become implanted, and because of this contamination of the tumor bed, a recurrence results. Of the 21 persons operated on by enucleation, only 12 were cured. Among those cured, enucleation in 1 was reinforced by the use of

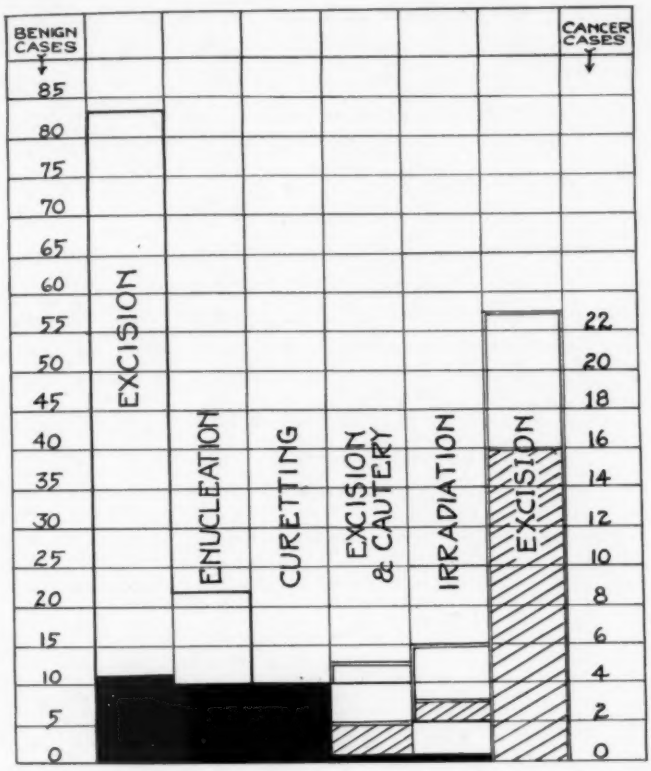

Fig. 15.—Chart showing the results of treatment in tumors of the parotid gland. To the left is shown results of treatment in the benign tumors and to the right the results of treatment in malignant tumors. The recurrences of the benign growths are indicated in black; the deaths in the cases of malignant tumors are indicated by the diagonal lines.

the cautery. In the others, it is practically certain that the enucleation was carried out without serious damage to the capsular structures.

Frequently the fibrous structures about these tumors appear to be bound down to the ramus of the jaw and to be intimately connected with the parotid gland, and often closely bound to the facial nerve. It is apparently when the mass is freed from these structures that implantation leading to recurrence takes place. One should attempt

TABLE 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid*

Path. No.	Age	Duration, Mos.	Treatment	Date of Operation	Result
48157	39	72	Complete excision; capsule ruptured; ether placed in wound for recurrence; other operation 5 yrs. before; growth again 1 yr. ago	9/30/30	Oct., 1931: Well, but recurrence of tumor locally
47439	57	120	Complete excision with healthy margin	5/21/30	Oct., 1931: Well; no recurrence; well 1 yr. 5 mos.
46839	28	108	Excised piecemeal	2/ 8/30	Oct., 1931: Recurrence, general health good
46109	77	504	Enucleation; capsule damaged	1929	Oct. 25, 1931: Well; no recurrence
45609	70	12	Enucleation; alcohol placed in tumor bed	6/19/29	Oct., 1931: Well; no recurrence, 2 yrs. 3 mos.
43650	..	6	Excision	9/15/30	Aug., 1931: Facial paralysis; no recurrence following operation for recurrence 6/15/31
42968	54	72	Complete excision with parotid margin	1927	July 6, 1931: Well; no recurrence
42469	52	51	Complete excision with margin gland (then radiation) radium	12/ 2/27	
42317	55	216	Complete excision of tumor; no capsule damage	10/28/27	Oct., 1931: Well; no recurrence
42218	43	...	Complete excision; also radiation; radium	11/ 1/29	Aug., 1931: Well 1 yr. 9 mos.; no recurrence
42204	..	...	Complete excision	5/19/21	Aug., 1931: Well; no recurrence
41900	28	48	Complete excision; no capsule damage	6/25/29	Aug., 1931: Well; no recurrence
41862	..	42	Complete excision with healthy gland margin	4/19/29	July, 1931: Well; no recurrence
41699	25	60	Wide excision, phenolization..		
41496	65	24	Complete excision with surrounding margin for recurrence from operation 2 mos. earlier	4/ 4/29	Oct., 1931: Well; no recurrence
41330	22	43	Complete excision	2/ 4/29	Aug., 1931: Well; no recurrence
41273	20	24	Complete excision	4/27/27	
41218	57	...	Lumps appeared suddenly; decreased half under x-ray; completely excised	12/20/28	July 21, 1931: Well; no recurrence
40914	39	2	Complete excision for recurrence, 2 mos. following first operation	10/ 2/28	June, 1930: Well; no recurrence
38690	18	4	Enucleation three times.....	Sept., 1926-Feb., 1927	Aug., 1931: Recurrence; intensive radium treatment continued
38454	18	25	Complete excision with cautery; use of zinc chloride and alcohol	.....	Sept. 4, 1926: Recurrence; reoperated on 11/1/26
38336	24	24	Complete excision with cautery of most of gland; ligation of duct	Nov., 1926	
38136	72	156	Excision	1926	Oct., 1931: Patient reported having died in 1930, 4 yrs. after operation; cause not stated
36730	38	48	Bilateral ligation of external carotids	11/ 6/30	Radiation caused no decrease of tumor; health poor
36438	19	14	Enucleation; capsule intact...	11/24/24	Jan., 1931: Well; no recurrence
36060	58	20	Complete excision for recurrence after 2 yrs. postoperatively	Nov., 1924	Oct., 1931: Well; no recurrence; basal cell features
36058	..	108	Complete excision for recurrence 9 yrs. after first operation	Nov., 1924	Aug., 1931: Well; no recurrence
35588	26	96	Complete excision with wide margin	6/11/24	Aug., 1931: Lower facial paralysis; well; no recurrence
35501	31	120	Complete excision with parotid margin	May, 1924	Partial facial paralysis; no word since
35308	62	24	Complete excision with parotid margin	3/12/24	Sept., 1931: Well; no recurrence

TABLE 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid —Continued*

Path. No.	Age	Duration, Mos.	Treatment	Date of Operation	Result
35113	48	2	Complete excision with gland margin for recurrence after 10 yrs.	3/13/24	Oct., 1931: Well; no recurrence
31593	52	120	Complete excision, third operation	4/11/29	No recurrence; died 22 mos. after operation, 6/2/31, of pneumonia
31384	58	...	Complete excision with gland margin	10/13/22	Oct., 1931: Well; no recurrence; numbness of tongue; paralysis of lips
28353	35	...	Complete excision third operation	.....	July 15, 1921: Died of septicemia several days following operation
28324	23	...	Complete excision with gland margin	6/13/21	Well 4 yrs. 2 mos. later
28313	44	120	Complete excision	3/21/21	July, 1931: Well; no recurrence
28174	19	11	Enucleation; no capsule damage	May, 1921	Well, 1 mo. later
28078	28	36	Enucleation, capsule damaged	5/ 6/21	Jan., 1921: Well
27175	38	120	Complete excision with gland margin	Dec., 1920	March, 1921: Well; no recurrence
27014	60	96	Complete excision	Oct., 1920	Sept., 1929: Well; no recurrence; basal cell features
26856	61	24	Radiation	Sept., 1920	Oct., 1920: Tumor mass shrunken; abscess formation; death of cardiac decomposition Nov. 20, 1920
26732	29	30	Complete excision with gland margin	Oct., 1920	July, 1931: Well; no recurrence
26349	..	156	Excision for recurrence of tumor 15 yrs. after first operation	1920	Oct., 1931: Well; no recurrence
26213	50	168	Complete excision with gland margin	6/ 3/20	July, 1931: Well; no recurrence; complete facial paralysis since operation
25945	23	60	Excision piecemeal	4/16/20	Aug., 1921: Recurrence
23480	31	120	Complete excision with gland margin	July, 1918	Well, 1919; no recurrence
23146	40	36	Excision piecemeal with cautery; second operation	1/19/21	July 19, 1921: Facial paralysis; no recurrence; well
23032	27	60	Complete excision gland margin	4/10/18	April, 1919: Well; no recurrence
22695	45	16	Excision for recurrence 2 yrs. after first operation	Feb., 1918	Sept., 1931: Well; no recurrence
22579	66	9	Complete excision gland margin, third operation	Dec., 1917	Feb., 1926: Died of thrombo-angiitis obliterans and gangrene 8 yrs. 2 mos. after operation; no recurrence of tumor
22478	56	192	Excision; no capsule damage	11/13/17	Nov., 1919: Well; no recurrence
21990	60	240	Complete excision with cautery	8/14/17	Jan. 19, 1928: Death 10½ yrs. following operation
21110	58	2	Complete excision with cautery	3/ 8/17	May, 1918: Dead 14 mos. after operation, result of prostatic hypertrophy; no recurrence
20872	..	...	Complete excision	.....	1931: Dead several years later, cause unknown
20163	..	156	Complete excision; no capsule damage	9/13/16	April, 1919: No recurrence; epilepsy, 1931; death about 15 yrs. following operation from unknown cause
19866	31	84	Complete excision	7/20/16	March 24, 1930: Dead of pelvic carcinoma 3 yrs. and 8 mos. following operation; parotid growth had not recurred

TABLE 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid —Continued*

Path. No.	Age	Duration, Mos.	Treatment	Date of Operation	Result
18295	45	96	Complete excision; third operation	Oct., 1915	Sept., 1931: Cysts in tumor area; facial paralyses have not increased in size since present 14 yrs. ago
17211	25	...	Excision; third operation....	3/22/15	Paralysis of face, no recurrence; committed suicide March, 1930, 15 yrs. following operation
17105	42	36	Complete excision; capsule damaged in wound	3/ 6/15	
16629	54	264	Enucleation; no capsule damage	12/12/14	Oct., 1931: Well; no recurrence
16543	44	144	Complete enucleation, no capsule damage	Oct., 1914	1919: Well; no recurrence
16467	21	84	Complete excision; no capsule damage	10/31/14	April, 1919: Well; no recurrence
16272	38	100	Complete excision; curettage	9/21/14	July, 1921: Well; no recurrence
16208	27	132	Complete excision; no capsule damage	9/ 5/14	April, 1919: Well; no recurrence
15233	..	84	Complete excision	Jan., 1914	May, 1919: Well; no recurrence
14695	52	360	Complete excision	9/27/13	May, 1919: Well; no recurrence
14689	77	8	Complete excision of tumor and gland margin with cautery for recurrence	7/13/25	1929: Well; no recurrence; conjunc. initiation secondary to facial paralysis
13575	45	7	Complete excision with cautery	12/14/12	1919: Well; no recurrence
12675	27	132	Complete excision with surrounding margin	4/20/12	1918; Well; no recurrence; Sept., 1931: well few years ago
12460	59	96	Excision with ligation of common carotid	2/20/12	Feb. 21, 1912: Dead from postoperative shock
12291	42	24	Complete excision for recurrence	12/16/11	Facial paralysis; Sept., 1931: well; no recurrence
11048	27	24	Enucleation for recurrence....	12/29/10	1912: Died during operation for recurrence
10031	36	60	Complete excision with margin for recurrence	10/16/09	May, 1919: Well; no recurrence
9784	54	2	Complete excision, cauterization and phenolization because of capsule rupture	5/27/09	Nov., 1920: Well; no recurrence
9518	40	24	Complete excision; capsule rupture; cauterization and phenolization	2/11/09	Oct., 1931: Well; no recurrence
9494	25	84	Complete excision; capsule rupture; cauterization and phenolization	2/ 1/09	Oct., 1931: Well; no recurrence
8989	57	36	Complete excision	6/ 8/08	1915: Killed in accident 7 yrs. after operation; no recurrence
8171	43	144	Complete excision	5/ 3/07	Oct., 1915: Well; no recurrence
8131	70	120	Enucleation; no capsule damage	4/19/07	1908: Well; dead before 1913, probably from apoplexy since patient had one stroke before operation; no record of recurrence
8127	72	216	Excision of parotid gland and chiseling away of ramus of the jaw	.....	June 15, 1908: Death of chronic nephritis 1 yr. 4 mos. after operation; recurrence of tumor locally
7972	58	300	Complete excision	2/21/07	Feb. 21, 1907: Dead of bronchopneumonia
6706	69	240	Complete excision	9/13/05	June, 1907: Well; no recurrence; dead by 1928, cause unknown
6586	47	216	Excision piecemeal 2 yrs. after first operation for recurrence	1905	1915: Well 10 yrs., then recurrence; third operation June, 1920

TABLE 1.—*Results of Treatment in Benign Mixed Tumors of the Parotid —Continued*

Path. No.	Age	Duration, Mos.	Treatment	Date of Operation	Result
5490	45	156	Tracheotomy and enucleation; no capsule damage	5/18/04	Sept., 1907: No recurrence; chronic nephritis
5417	17	12	Complete excision	4/15/04	1908: Well; died of extensive recurrent tumor locally 9 yrs. following operation; no evidence of metastases
5167	65	36	Complete excision piecemeal by curettage	11/20/03	March, 1908: Well; death in 1909, 4 yrs and 4 mos. after operation; recurrence; blindness 8 mos. preceding death
5044	43	36	Complete excision for recurrence within 1 yr.	1/ 5/04	Oct., 1931: Well: no recurrence; 50 per cent facial paralysis
5009	60	576	Complete excision with gland margin	8/24/03	July, 1907: Well; no recurrence
4872	47	48	Complete excision	5/21/02	Oct., 1931: Well; no recurrence
4861	24	100	Complete excision	6/ 1/03	1908: Well; no recurrence
4297	17	24	Complete excision, gland margin	6/ 6/02	1916: Well; no recurrence
4231	77	540	Excision	4/29/02	1908: Dead due to other causes 6 yrs. after operation; no recurrence
4227	35	108	Complete excision; resection, wiring of lower jaw and tracheotomy	4/20/02	1919: Dead from apoplexy 17 yrs. after operation; no recurrence of tumor
4040	58	240	Complete excision; facial nerve cut; also second operation	11/27/01	1910: Recurrence; 1919: well; no recurrence
3973	20	240	Enucleation	11/ 9/01	1910: Well; then recurrence
			Complete excision	6/ 8/10	1919: Well; no recurrence
3282	27	108	Complete excision	9/13/00	March, 1908: Well; no recurrence
3051	53	60	Complete excision; enucleation	4/24/00	Oct., 1913: Well; no recurrence
2911	21	84	Complete excision	1/19/00	1905: Well; no recurrence; temporary facial paralysis after operation
2756	53	72	Enucleation: division of parotid duct	10/06/99	1905: Recurrence
2173	56	324	Enucleation; ligation of jugular vein	4/15/98	1908: Died of other causes 10 yrs. after operation; no recurrence
1669	31	276	Complete excision	1/26/97	1905: Death of pneumonia 5 yrs. after operation; no recurrence
1578	26	120	Complete excision with gland margin	11/13/96	1919: Well; no recurrence; facial paralysis
S.N. 1491	55	120	Enucleation; no capsule damage	3/15/92	1915: Death from apoplexy 23 yrs. after operation; no recurrence of tumor
S.N. 1095	27	36	Complete excision	7/27/91	April, 1908: Well; no recurrence
997	40	48	Complete excision; ligation of external carotid	7/19/95	Oct., 1931: Well: no recurrence
803	20	24	Complete enucleation	3/ 9/95	June, 1897: Death 2 yrs. later following abdominal condition; no recurrence
S.N. 740	26	60	Complete excision with surrounding glands	12/ 2/90	April, 1919: Well; no recurrence
605	23	96	Complete excision with gland margin	10/15/94	1908: Well; no recurrence; partial loss of sight of right eye and of hearing in right ear

TABLE 2.—*Results of Treatment in Carcinoma of the Parotid*

Path. No.	Age	Duration, Mos.	Treatment	Date of Operation	Result	Time Well
43232	10	..	Incomplete excision; radium packs applied 3 times; no result; recurrence	Jan., 1930	Oct. 20, 1931: General condition good; no metastasis; no increase in size of recurrent growth; radium pack continued	1 yr. 9 mos.
42355	55	10	11/5/27: Second radical mastoidectomy; tumor material curetted out	11/ 5/27	Jan. 1, 1928: Died of pressure symptoms on brain; emanations for 8 hrs. had been of no value	2 mos.
41752	42	6	Complete excision with wide margin, cautery and knife	5/28/29	Sept., 1931: Well; no recurrence	2 yrs. 4 mos.
39344	30	3	Piece of tumor removed following excision of glands in neck and recurrence 2 mos. before; radium advised	April, 1916	Aug. 5, 1916: Death 4 mos. after operation much pain and distress	
36754	42	44	Complete dissection of scar, sternocleidomastoid muscle, internal jugular vein and all glands for recurrence	6/17/25	May, 1931: Poor health, great pain locally; recurrence last 3 yrs.; anemia, phlebitis left leg and gastro-intestinal upset	
36054	47	84	Excision of tumor 6 yrs. ago; recurrence 6 mos.; 5 series of x-ray treatments	1924-26	Aug., 1931: Death; carcinoma of large intestine; no recurrence of parotid tumor following disappearance on x-ray treatment	5 yrs.
35408	67	300	Complete excision of parotid area of skin; knife and cautery; 3 x-ray treatments before of no avail; recurrence after second operation for benign tumor; first 25 yrs. ago; second 10 yrs. ago; facial paralysis, 6 mos.	5/29/24	July 29, 1924: Dead	2 mos.
27755	50	36	Complete excision	Feb., 1921	Aug., 1921: Died 6 mos. following operation; huge recurrence	
27368	39	36	Complete excision with cautery; parotid gland removed in toto; division of 7th nerve	1/ 6/21	July, 1921: Well; no recurrence; facial paralysis	6 mos.
24680	42	144	Excision of mass posterior to parotid gland, into neck and about carotid artery	6/18/14	Aug. 17, 1919: Death; suffered a left hemiplegia immediately after operation; never rallied	
22521	59	8	Complete excision with parotid gland; cautery used	11/27/17	1921: Well; no recurrence	4 yrs.
21549	62	24	Complete excision of tumor and gland margin with cautery	5/18/17	April, 1919: Recurrence; quite ill; Oct., 1931: letter returned; patient dead; cause unknown	2 yrs.
1153	14	8	Complete excision of tumor and gland margin with cautery; also phenolization of tumor bed for recurrence	7/ 5/11	Patient died shortly thereafter; cause unknown	
9896	67	4	Complete excision	8/13/09	1912: Patient died; exact cause unknown	3 yrs.
9223	45	60	Complete excision; ligation of jugular vein for recurrence	9/15/08	1913: Recurrence; axillary mediast. metastasis in a few months; death about 5 yrs. following operation	
9216	33	4	Complete excision	9/11/08	Oct., 1931: Well; no recurrence	23 yrs.

TABLE 2.—*Results of Treatment in Carcinoma of the Parotid—Continued*

Path. No.	Age	Duration, Mos.	Treatment	Date of Operation	Result	Time Well
9120	45	40	Irradiation; tracheotomy	Feb., 1926	Feb. 24, 1926: Death 1 mo. following treatment due to aspiration pneumonia and metastases	
8771	57	8	Complete excision with gland margin	2/20/08	Dead, date and cause unknown	
7909	61	144	Excision of tumor with part of ear and parotid	2/21/07	Sept. 20, 1908: patient dead	1 yr. 6 mos.
7547	62	12	Excision of tumor, intrajugular vein, external carotid artery, sternomastoid muscle and glands of neck	9/12/06	Feb., 1908: Death; local recurrence and internal metastases	1 yr. +
6798	..	..	Excision of tumor.....	1905	1913: Patient dead; cause unknown	8 yrs.
6468	44	10	Excision of tumor with portion of parotid, submaxillary gland and lymph glands of neck	6/15/05	1915: Well; though local recurrence since 1908	10 yrs.
5686	63	1	Excision of lymph glands of neck; because of involvement of glands, parotid tumor was not touched	1904	1905: Death 9 mos. after operation; x-ray caused parotid to disappear, but at death there was marked glandular enlargement and ascites	9 mos.
4736	58	2	Complete excision of tumor with glands of neck; excision of glands of neck	3/24/03 5/ 2/03	Sept. 15, 1903: Death, exact cause unknown	5 mos.
4322	28	15	Excision of tumor with overlying skin, also of gland along sternomastoid muscle	6/23/02	July, 1902: Partial facial paralysis; no note since	
3187	31	5	Excision of tumor of parotid and phenolization, secondary to scaly condition of lobe of ear	6/29/01	June 9, 1902: Recurrence of tumor; inoperable	1 yr.
2502	53	24	Complete excision of mass with parotid tissue and lymph glands; facial nerve divided	3/17/99	Feb., 1900: Death 11 mos. after operation; obscure general asthenia	11 mos.
2132	74	1	Excision of tumor, skin and parotid tissue	3/ 4/98	Dead; partial facial paralysis after operation	
1427	48	14	Excision of recurrent tumor and glands of neck 1 mo. after first operation	7/21/96	1897: Patient dead 1 yr. after operation; cachexia and cerebral symptoms	

to free the nerve, but care must be taken to see that it is not at the risk of recurrence. As Ochsner [39] pointed out, this is best accomplished by making a wide incision so that sufficient exposure is obtained, and then if any radicles appear to be adherent to any particular degree a proper dissection is more readily carried out.

A better method of treatment as attested by the results reported here is that of complete excision by sharp dissection. If the patient is seen early enough and the tumor has not yet become too large, this can be done effectively, a margin of healthy tissue about the capsule being included. In the smaller growths this gives assurance of a cure and

39. Ochsner, A. J.: Three Cases of Benign Lesions of Parotid Gland, Surg. Clin. Chicago **3**:903 (Aug.) 1919.

offers the probability of no attending damage to the seventh nerve. Even if the mass has reached a rather large size, this method still offers hope of success, though there is a greater possibility of facial paralysis. In 83 persons treated in this manner, both with benign and with malignant tumors, there were 72 cures and 11 recurrences. Certainly this is as good a method as one could desire for the primary tumors. It is particularly efficacious when coupled with phenolization or the use of a 50 per cent solution of zinc chloride.

The most radical method, attended usually with even a higher percentage of cures than the foregoing one, is the use of the cautery to excise the tumor completely and widely. There are always much scarring and mutilation with this method, and practically invariably a facial paralysis. Of course, the percentage of cures is greater than by the other methods, and it may be the method of choice in the cases of recurrent tumors in which there is already a facial paralysis. If the tumor bed is thoroughly coagulated, there is no necessity for the use of chemical cauterization, but this may be used as an added precaution. When it has been used there have been good results.

Irradiation.—In mixed tumors irradiation in association with operation was attempted in 3 cases in this series. In 2 there was benefit, although it is doubtful how much credit may be ascribed to the operation and how much to the irradiation. At the Howard Kelly Hospital (Baltimore), irradiation of mixed tumors has not been highly successful in the past for the following possible reasons:

1. The tumor cells are too resistant.

2. The position of the gland in the parotid region does not lend itself well to cross-irradiation, so that very heavy doses cannot be administered without great damage to the skin.

3. Implants of radium may injure the facial nerve because of the close proximity of the implants to the nerve. For this reason, in a mixed tumor which can definitely be cured by complete excision, radium is less the instrument of choice than surgical intervention.

Large doses of external irradiation with a radium pack just within the limits of an erythema dose from several directions over a long period of time have been found to be of some benefit in isolated cases. In 1 case irradiation was carried out at weekly intervals for six months, and the tumor mass in that period of time was found to have been reduced from 5 cm. to 3 cm. in diameter. Implantation of radon has been attempted in some instances with good results over a period of from two to three years. This offers a palliative treatment of mixed tumors by irradiation, and in those persons who would prefer this to

the chance of operative complications as exemplified by facial paralysis or the much rarer salivary fistula, this may be carried out. Mixed tumors, however, may resume growth after reacting favorably for a time to external or interstitial irradiation.

In cases of carcinoma of the parotid, irradiation has been found to be of distinct advantage. In 1 case, clinically diagnosed as carcinoma, a huge infiltrating growth was nonencapsulated and attached to the surrounding structures. This neoplasm involved the whole gland, ear and mastoid region in a rapidly growing mass. Even the most radical opera-

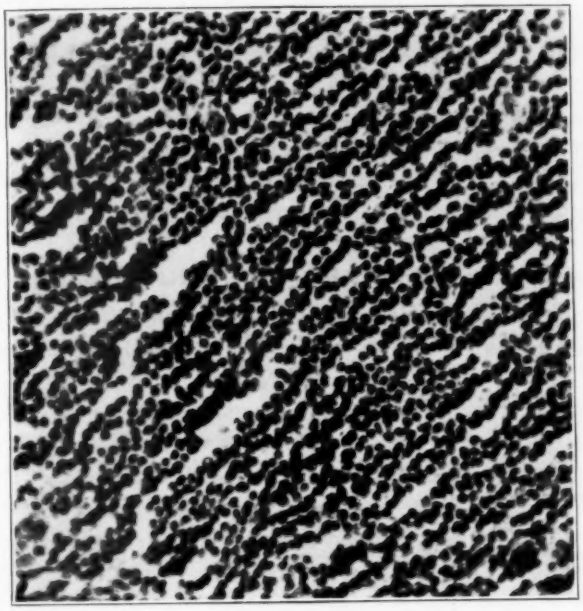

Fig. 16 (path. no. 36054).—Lymphosarcoma of parotid gland. A white man of 47 had a tumor of seven years' duration which recurred in spite of excision and high voltage roentgen therapy. Four series of high voltage roentgen treatments caused the ultimate disappearance of the parotid tumor and the enlarged cervical nodes. The patient died five years later of a so-called carcinoma of the large intestines. No autopsy was performed. The photomicrograph shows diffuse invasion of the parotid gland by typical lymphosarcoma.

tion offered little prospect of success. This tumor responded to the external application of radium. Rapid reduction in size was noted within two weeks, and soon the mass disappeared entirely. This patient has remained well three years.

In the series of cases of malignant growths in which radium therapy was attempted most of the lesions were advanced and many recurrent when the patients were first admitted to this hospital, and the treatment was combined with operation. One growth, which had recurred after an

incomplete operation, diminished slightly in size, and has been kept under control since, for a period of a year and a half, by repeated irradiation with radium packs. In 3 cases irradiation proved to be of no avail. However, in a case in which there was a recurrence six months after radical operation, roentgen therapy caused a disappearance of the growth, and the patient remained well for five years and died later supposedly of carcinoma of the intestine. Examination of the section showed the tumor to be lymphosarcoma (fig. 16).

The best results so far obtained by irradiation have been with the small round, cuboidal or spindle cell carcinoma of Chevassu—a malignant variant that has frequently been termed sarcoma. These cases yield favorably to irradiation, and good results may be seen within two weeks.

Secondary carcinomas of the parotid, particularly such tumors as those primary in the testicle and of embryonal type, melt rapidly under irradiation. Success may also be achieved in squamous cell carcinomas invading the parotid from the adjacent areas of skin.

CHOICE BETWEEN SURGICAL INTERVENTION AND IRRADIATION

The data on treatment in the present series of cases indicate the value of the judicious use of both irradiation and surgical intervention in tumors of the parotid gland. It is important in selecting the mode of treatment to distinguish between primary and recurrent tumors and between benign mixed tumors and carcinoma of the parotid. In small primary benign tumors complete excision by sharp dissection is the method of choice if this can be accomplished without danger to the facial nerve. In tumors that are infiltrating and malignant, a preliminary course of high voltage roentgen therapy should be given and a similar course of irradiation in all borderline tumors in which carcinoma is suspected. If shrinkage of the tumor occurs, substantiating the opinion of basal cell cancer, external irradiation should not be continued but should be followed by excision. In all recurrent tumors it would seem advisable also to administer a preliminary course of external irradiation for a short time (from four to six weeks). This should be followed by excision if the tumor is deemed operable, otherwise irradiation may be continued as a palliative measure, and in such cases there is no objection to fortifying the treatment by the implantation of radon. Where the tumor is under control with external irradiation, the danger of injury to the facial nerve must be considered before additional therapy is attempted in the form of surgical procedures or interstitial irradiation.

When excision of benign, recurrent or malignant tumors is attempted, with or without preliminary irradiation, the question arises

whether the tumor bed following excision should be cauterized or should receive irradiation.

Considering all the available data, the matter of combining roentgen therapy and surgical treatment can be summed up for the present as follows: Complete excision should be chosen for all benign operable tumors and irradiation as a palliative measure in all inoperable cases. In borderline cases, in recurrent tumors and in carcinoma of the parotid, external irradiation should be given as a therapeutic test or as preliminary treatment, followed by excision, reenforced with interstitial irradiation of the tumor bed in recurrent or malignant cases.

PRESERVATION OR SACRIFICE OF THE FACIAL NERVE

Besides the alternative between surgical intervention and irradiation, the question of preservation of the facial nerve must be kept constantly in mind in the treatment of parotid tumors. If the tumor is primary and benign and excision is determined on, should the operator in his dissection complete the removal of the tumor with the inclusion of a healthy margin when important nerve radicals pass into the tumor substance? Or should an attempt be made to spare the nerve by bisecting the tumor at this point, peeling it from the nerve and after the operation cauterizing the tumor bed with chemical applications such as a 50 per cent solution of zinc chloride or implanting radon seeds in the tumor bed? The latter procedures may be justified if the major radicals supplying the eye and the entire side of the face are involved, whereas a lower or less important filament may be sacrificed. Whether the prevention of deformity is worth the chance of recurrence must be decided by the surgeon in charge after a careful consideration of such factors as the age and sex of the patient, the social status and the microscopic structure of the tumor. In certain cases it may be advisable to postpone operation and attempt to control the tumor by external irradiation.

However, in all recurrent tumors and in all rapidly enlarging tumors with malignant features, the treatment should aim at eradicating the disease without regard to preservation of the nerve. The basis for this decision is the almost inevitable sacrifice of the nerve eventually with subsequent recurrences.

SUMMARY

The greater number of tumors of the parotid gland may readily be divided into benign mixed tumors and malignant basal cell neoplasms. The benign lesions are more frequent (83 per cent), occur in younger persons (from 21 to 45 years), have a slower rate of growth (average duration, eight years) and are usually circumscribed, firm, rubbery growths which on microscopic section have a large amount of connective

tissue and myxomatous stroma. The malignant lesions are less common (17 per cent), usually occur in persons over the age of 45 (from 45 to 65 years), have a more rapid rate of growth (average duration, four years) and are adherent, hard or soft growths which on microscopic examination have adenocystic basal cell features. The growths with basal cell features are more prone to recur after treatment. The benign mixed tumors are not truly mixed tumors but fibro-adenomas of the parotid gland in which the stroma is acted on by a salivary secretion from the adenomatous areas to produce the myxomatous or cartilaginous features.

Both surgical intervention and irradiation have their place in the treatment of these tumors. Small benign mixed tumors are best treated by complete excision with the knife, care being taken to preserve the facial nerve. The malignant tumors should be irradiated first and later excised if they become operable and freely movable. Otherwise palliative irradiation should be continued. Following the excision in operable cases, interstitial irradiation may be applied to the tumor bed.

Assistance was received from Dr. Curtis Burnam of Baltimore and Dr. Murray Copeland, Memorial Hospital, New York City, on the use of irradiation in parotid tumors, and Dr. W. C. Caldwell compiled the data on the earlier cases recorded in this laboratory.

COMPLETE REMOVAL OF TWO TUMORS OF THE THIRD VENTRICLE WITH RECOVERY

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The literature pertaining to tumors of the third ventricle is largely concerned with the various clinical syndromes, postmortem observations and histologic studies of the lesions and, only recently, with preoperative diagnosis and surgical removal of the new growths. It is not my purpose in this paper to give a résumé of the literature on the numerous clinical syndromes caused by tumors of the third ventricle, which have been so ably described by Weisenburg and by several others.[1]

As regards the early diagnosis of these lesions, one finds that the injection of air into the ventricles either by the direct or by the lumbar route, as first described by Dandy[2] in 1918 and 1919, respectively, is of the greatest help. Furthermore, the injection of dye into one lateral ventricle to determine the patency of the foramina of Monro has also contributed to the diagnosis of lesions obstructing one or both of these openings.

The successful treatment in the case herewith reported may not be applicable in every instance, so that no claim will be made that the technic employed is of general application or that all tumors of the third ventricle irrespective of their pathologic character are amenable to surgical attack.

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REPORT OF CASES

CASE 1.—*History.*—E. W., aged 20, from the neurologic service of Dr. Robert F. Sheehan, was admitted to Community Hospital on Sept. 23, 1932, and discharged on November 6. She was referred by Dr. C. S. Mirkin, who had treated her since 1930 for headache and tinnitus and nausea and vomiting in the morning. Her first symptom was a hammering sensation referred to the left vertex, which lasted for several weeks. There was diplopia for about three weeks during the first year of illness. In 1930, a lumbar puncture was performed which relieved her from all symptoms for one year. With the return of symptoms in November, 1931, frontal headaches were more pronounced than they had been previously and were noticeably worse a few days before the menstrual periods. The patient recalled having fainted three times and ascribed the attacks to her menstrual periods. On September 12, her physician performed a lumbar puncture which gave relief from symptoms for one week. Owing to the recurrence of symptoms, she was admitted to the hospital on September 23.

As a child she had suffered from measles, whooping cough, diphtheria and scarlet fever. Her family history did not indicate any nervous or mental disease.

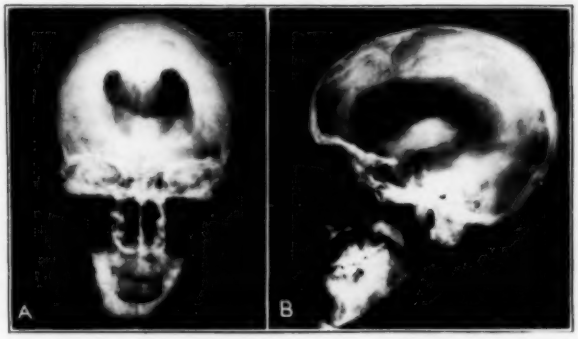

Fig. 1.—*A*, anteroposterior view showing the absence of a shadow of the third ventricle and curved deformities in the mesial inferior extent of both lateral ventricles. *B*, lateral view, showing markedly dilated lateral ventricles with no shadow representing the third ventricle.

Examination.—The patient was rather delicately built and was fairly well nourished, with no abnormal attitudes or deformities. She stood normally with eyes opened and closed, but in walking showed a tendency to fall to the left, especially on turning to the left. The nonequilibratory tests gave normal results. The deep reflexes were slightly increased in the left upper extremity, but in the lower extremities they were equally active; there were no abnormal reflexes. Her motor and sensory status was normal. The sense of smell was normal. The fundi showed some blurring of the disks save in a small temporal quadrant, where they were outlined; the veins were fuller than normal, but not tortuous. The visual acuity was 20/20, and the visual fields showed a slight enlargement of the blind-spots. The pupils were 5 mm. in diameter and reacted to light and in accommodation. The extra-ocular movements were normal save for a slight weakness of the right sixth nerve. The fifth and seventh nerves were normal. There was a mild middle ear deafness in the left ear; the right ear was normal, and the remaining cranial nerves showed no abnormalities.

Laboratory Examination.—The blood count showed a moderate secondary anemia. Urinalysis gave negative results. The spinal fluid was opalescent and contained 5 cells per cubic millimeter. The globulin test was negative; there was 25 mg. of protein per hundred cubic centimeters of fluid; the Wassermann reaction was negative, and the colloidal gold curve was 0-0. The Wassermann reaction of the blood was negative. Roentgenograms of the skull demonstrated no abnormalities other than a thinning of the dorsum sella. The manometric pressure of the spinal fluid was 580 mm. with the patient in the sitting posture. On October 6, roentgenograms taken after the removal of 78 cc. of fluid and the injection of 70 cc. of air by the lumbar route showed definitely dilated ventricles with poor visualization of the third ventricle. For this reason, ventriculography was carried out on October 11, with the patient under local anesthesia, according to the

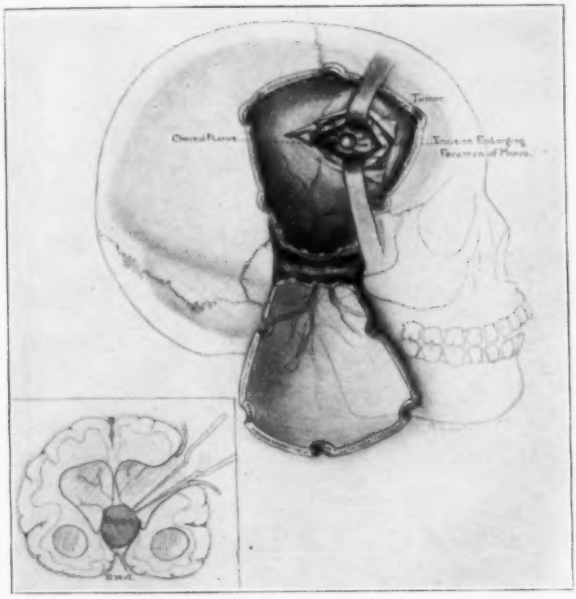

Fig. 2.—Lateral view showing the transcortical incision and exposure of the right foramen of Monro blocked by the tumor mass. Note that retraction was made upward and downward and not posteriorly, which would have endangered the motor cortex. The cross-section shows the manner in which the tumor capsule was delivered with a bayonet forceps through the enlarged foramen of Monro.

Frazier technic. The roentgenograms showed dilated lateral ventricles with the left larger than the right. The third ventricle was not shown, for there was a club-shaped defect in it, and the anteroposterior view showed a curved deformity in each lateral ventricle. These roentgenograms (fig. 1) warranted the diagnosis of a tumor of the third ventricle.

The results of the ventriculography were both interesting and significant. After trephination was done, the dura was felt to be under slightly increased pressure on both sides, and through stab wounds in the dura a brain needle was inserted into the right ventricle at a depth of 6 cm. and into the left at a depth of 4 cm.,

with the loss of a few cubic centimeters of fluid. Two cubic centimeters of indigo carmine dye was injected into the right ventricle and, after several minutes, a small amount of blue-tinged cerebrospinal fluid escaped from the needle in the left ventricle. Then the flow of blue-tinged fluid stopped, and the remaining fluid obtained from the left ventricle was clear and colorless. The fluid obtained from the right ventricle was of a deep blue. In all, 75 cc. was removed from the left ventricle and 27 cc. from the right. When a satisfactory replacement of air had taken place, the needles were withdrawn and the wounds closed. Since little dye entered the left ventricle by way of the foramina of Monro and the third ventricle, a ball valve closure of one or of both foramina was indicated. That the obstruction was not complete was also borne out by the patient's lack of papilledema and of signs of marked increased intracranial pressure.

Fig. 3.—Low power photomicrograph showing the contents of the cyst. Clefts filled with cholesterol crystals are seen in an amorphous eosinophilic material; the clefts in many instances are surrounded by giant cells.

The history and the few neurologic findings pointed to a midline lesion. However, the information gained during ventriculography and by examination of the plates led to a definite diagnosis of a tumor of the third ventricle. On October 15, with the patient under avertin anesthesia, a right osteoplastic flap was turned down without incident. The dura was tense and not pulsating. Through a stab wound in the dura a brain needle was entered into the right lateral ventricle, allowing the escape of air and thereby greatly reducing the intracranial pressure. The dura was opened in the anterior upper extent of the exposure horizontally from 3 to 4 cm. Then a vertical incision 1.5 cm. in length was made in the dura at right angles to the anterior extent of the horizontal incision, exposing a small triangular area of cortex.

The larger cortical vessels were controlled by clips, following which a horizontal transcortical incision 3.5 cm. in length was made by means of a high frequency

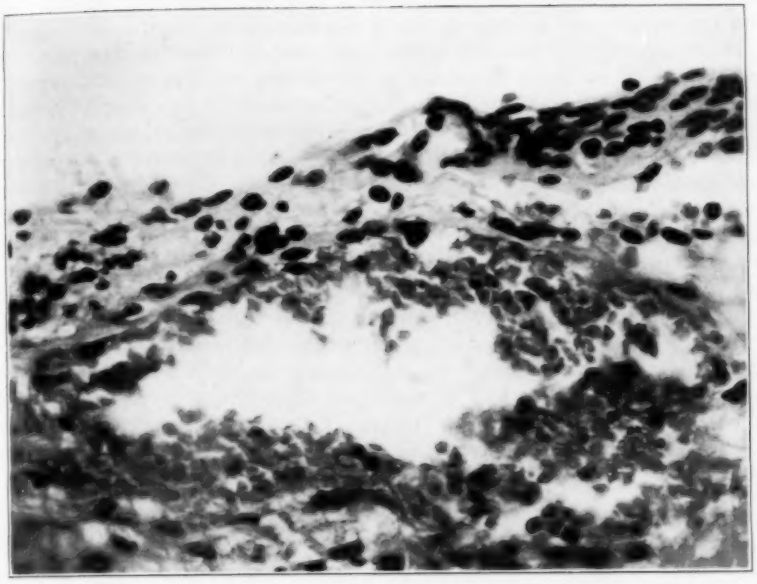

Fig. 4.—High power photomicrograph showing squamous epithelium lining the cyst.

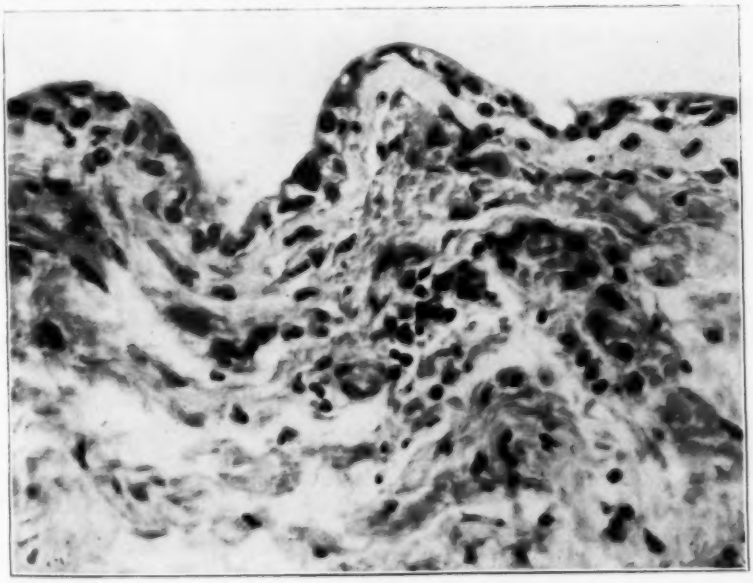

Fig. 5.—Photomicrograph showing a single layer of epithelium lining most of the wall of the cyst, with an infiltrated layer of heavy connective tissue beneath.

knife. The remainder of the transcortical incision was carried out with blunt dissection opening into the anterior extent of the right lateral ventricle. By means of brain retractors, one retracting upward and one downward, a good view of the mesial wall of the right lateral ventricle was obtained, and a little farther posteriorly an enlarged right foramen of Monro was brought into view. The foramen was blocked by a round, bluish mass together with a piece of choroid plexus which came through the posterior extent of the opening (fig. 2). Several veins running along the mesial wall of the ventricle were clipped, and the foramen, which was 1 cm. in diameter, was enlarged anteriorly for a distance of 1 cm. by the use of electrocautery. The choroid plexus was adherent to the capsule of the tumor at the foramen of Monro, and before it was free from the tumor a clip was placed on the choroid to control bleeding. A stab wound was made into the presenting portion of the tumor, allowing about 2 drachms (7.5 cc.) of dirty, greenish-yellow material to exude, which was sucked away. On examination, the material was found to be largely crystals of cholesterol. After the greater part of the contents of the tumor was removed, that portion of the growth which seemed to be free was carefully brought through the enlarged foramen of Monro. A pedicle 4 mm. in diameter composed of whitish tissue containing several blood

Fig. 6.—A snapshot of the patient taken two weeks after operation. The arrows indicate the outline of the flap.

vessels formed its attachment to the floor or to the right lateral wall of the third ventricle. The pedicle was clipped, and the tumor cut free. Finally, the entire tumor capsule, save for the initial opening made for the purpose of emptying its contents, was delivered intact by means of a bayonet forceps through the enlarged foramen of Monro. There was no troublesome bleeding throughout the procedure, and after free irrigation of the ventricles they were filled with physiologic solution of sodium chloride. The edges of the transcortical incision were laid in apposition, and the dura was closed with interrupted black silk sutures. There was no apparent edema of the brain; the intracranial tension was decreased, and, therefore, no decompression was necessary. The bone flap was returned to its former position and was closed in the usual manner with interrupted black silk sutures. Removal of the tumor was accomplished in a one-stage operation lasting two and a half hours.

Microscopic Description (figs. 3, 4 and 5).—The specimen was a cyst attached to a section of the choroid plexus. The wall of the cyst was lined on its inner surface by epithelium which was from two to four layers in thickness in some areas, where it was seen to be squamous in type. For the most part this epithelial lining was single-layered and composed of flattened or cuboidal cells, some of

which were vacuolated. Many of the cells contained keratohyaline granules. External to the epithelial layer was a band of heavy, collagenous connective tissue, which was somewhat edematous, showed many small hemorrhages and was mildly infiltrated by lymphocytes, large monocytes and a few polymorphonuclear leukocytes. Within the cyst was a large mass of homogeneous and granular eosinophilic material within which were numerous clefts filled with cholesterol crystals, the clefts being surrounded in many cases by foreign body giant cells. There was an ingrowth of capillaries and connective tissue into this central mass from the cyst at one point. In the contents of the cyst were also a considerable number of large mononuclear phagocytes containing hemosiderin. The diagnosis was epidermoid cyst.

Course.—Postoperatively, the patient was disoriented as to time but correctly oriented as to place and as to person. She talked somewhat irrationally for several days but within two weeks was approximately oriented and read the newspaper intelligently. The deep reflexes were increased on the left. There were slight left lower facial weakness and a decrease in strength of the grip of the left hand. However, the motor weakness disappeared at the end of the first week. She was able to sit up and walk about her room on the tenth day. On October 31, an encephalogram was made, 108 cc. of fluid being removed and an equal amount of air injected. With the patient in the sitting posture, the manometric pressure was 280 mm., which was 300 mm. less than the manometric pressure taken in the same manner before the tumor was removed. Air escaped over the cortex, and it was impossible to demonstrate any of the ventricles properly. The patient (fig. 6) was discharged on November 6 relieved of her former complaints. Her family physician reported that on November 21 he found that she had gained weight and strength to such an extent that she was able to play the piano for him and showed no mental disturbances. On Jan. 11, 1933, she returned to the follow-up clinic stating that she felt entirely well and had not felt so well for the past three years. There were no signs of organic neurologic involvement; vision was 20/20, and the fields were complete.

Dr. Cornelius G. Dyke assisted in the roentgenologic studies and Dr. Abner Wolf in the histologic work on the tumor that was removed.

This case demonstrates (1) the value of laboratory procedures in the early diagnosis of a tumor of the third ventricle; (2) that a tumor of the third ventricle may be removed in a one-stage operation and without the sacrifice of a large area of cortex, and (3) that the good postoperative result was due to the removal of the lesion before serious and irreparable injury to the brain had occurred directly by pressure or indirectly through the production of a marked hydrocephalus.

Case 2.—C. C., aged 33, was admitted to the Neurological Institute on April 28, 1933, and was discharged on June 4. The present illness began in 1928, when the patient suffered from severe frontal headaches which lasted a week. She remained well until March 5, 1933, when she again suffered from headaches and had a series of convulsions, the details of which were not available. After the convulsions vision began to fail and vomiting occurred irregularly for two weeks. Early in April, she was admitted to another hospital and was seen by me. Papilledema with hemorrhages was present, but no other definite signs were elicited, and a ventriculogram was decided on to localize the lesion. Since by this time the patient

felt better she left the hospital against advice and attended two other clinics before being admitted to the Neurological Institute. She was cheerful, able to walk about and free from all symptoms save impaired vision.

The patient's past history was unimportant. She had five healthy children. Her father died of pellagra and her mother died from an unknown cause. One brother and three sisters are living and well.

Neurologic examination revealed a well developed, well nourished woman who cooperated well and showed no abnormal attitudes or deformities save a midline abdominal scar of a previous appendectomy. Her gait and station were normal. There were no changes in coordination; skilled acts were normally performed, and there were no abnormal involuntary movements. The deep reflexes were slightly more active on the left than on the right side. The left lower abdominal reflex was the only one obtained. Plantar flexion was present, and there were no abnormal reflexes present. Motor power was preserved; the muscle status was normal; there were no signs of meningeal irritation, and the sensory status was

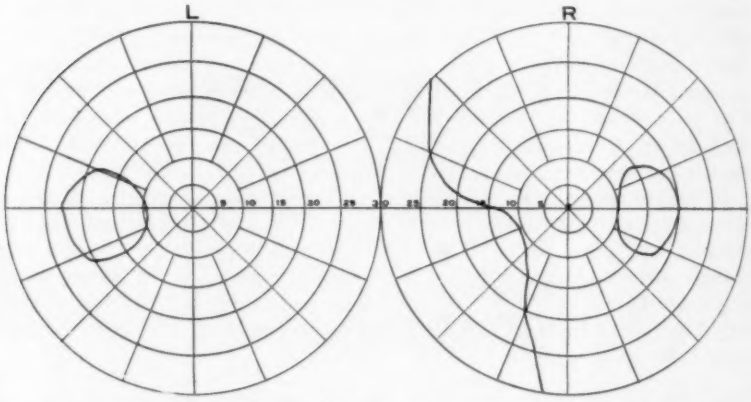

Fig. 7.—Visual fields on April 28, 1933, before operation: tangent screen, 1 meter; vision in the left eye, 20/50; in the right eye, 20/40; test object, 1 mm., white. The test was made in daylight, and the patient gave good cooperation.

normal. The cranial nerves were normal save for the presence of a papilledema of from 2 to 3 diopters. Vision in the right eye was 20/40, and in the left eye, 20/50. The visual fields (figs. 7 and 8) showed a lower nasal quadrant defect in the right field and bilateral enlarged blind spots.

The patient's mental status and laboratory status were normal. Roentgenograms of the skull showed the vault to be of average thickness and not unusual in size or shape. The floor and dorsum sellae were distinctly atrophic, and the posterior clinoids were slightly atrophic. Both mastoids were of average size, and the cells appeared clear. The pineal body was not visible. There was a small plaque of calcification in the meninges in the left posterior frontal region. The vascular channels and sutures did not appear abnormal. The sphenoid and petrous ridges appeared equal. The impression was that of an unlocalizable tumor of the brain, as indicated by the atrophic sella.

Clinically, the patient was considered to have either a tumor of the third ventricle or a bifrontal one, and therefore an injection of air was considered necessary. A ventriculogram was carried out on May 10, by means of bilateral punctures of

the posterior horns, at which time 55 cc. of fluid was removed from the right ventricle and about 110 cc. from the left ventricle. Air injected into one ventricle flowed freely from the needle in the other ventricle. The roentgenograms showed that both lateral ventricles were considerably dilated. They occupied their normal position. There was a concave margin to the medial aspect of the right lateral ventricle, demonstrating how a change in the pressure in one ventricle may alter the appearance of the medial aspect of the other ventricle. Only a small amount of air was noted in the third ventricle, and this was in the suprapineal recess. Both temporal horns appeared to be normal. The aqueduct and fourth ventricle were normal, and there was some air in the sulci, particularly over the left hemisphere. The impression was that there was a tumor of the third ventricle.

Since the diagnosis was definite from the laboratory standpoint and since this did not contradict the clinical findings, the patient was operated on for a tumor of the third ventricle. Only a partial first stage, right osteoplastic flap was accomplished under ether anesthesia. A general anesthetic was decided on because

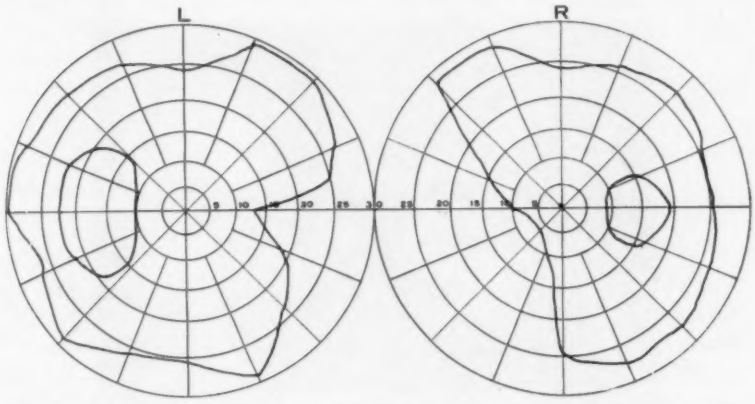

Fig. 8.—Visual fields on May 29, 1933, after operation: tangent screen, 2 meters; vision in the left eye, 15/40;. in the right eye, ability to count fingers at 20 feet; test object, 2 mm., white.

of the patient's poor cooperation and fatigue following ventriculography. A small anteriorly placed right flap was outlined and several trephine openings were made, when the patient's respirations became 60 per minute. The wound was therefore closed, and the patient returned to the ward to await a more favorable time to complete the operation.

On May 17, the patient was operated on again under local anesthesia. The bone flap was reflected without incident, and the dura found under moderately increased pressure. A horizontal incision 4 cm. in length was made in the dura over the middle of the right frontal lobe, 3 to 4 cm. from the sagittal sinus. The posterior extent of the incision was well anterior to the motor area. At right angles to the anterior end of the dural incision two vertical incisions each 1 cm. in length were made in the dura upward and downward. This exposed a triangular area of cortex with its base directed anteriorly. Two large cortical vessels were clipped, and the cortex was incised with a Bovie knife to a depth of 1 cm. for about the length of the horizontal dural incision. By blunt dissection, the remaining subcortical tissue was incised, and at a depth of 4 cm. the right lateral ventricle

was entered. To gain an exposure brain retractors were inserted, the incised brain tissue being held upward and downward so that no pressure was made at any time against the motor area. After the right lateral ventricle was emptied, the right foramen of Monro was readily seen, and just within was a round plum-colored mass. Dilated veins coursed along the mesial wall of the ventricle, and these, together with the choroid plexus extending forward, entered the foramen. With the Bovie knife, the foramen was enlarged anteriorly by an incision 0.5 cm. in depth. Several large veins were in danger of being injured, and those adjacent to the tumor were clipped. The choroid was found intimately attached to the tumor, and was clipped in two places as it entered the foramen, allowing the tumor to be cut free between the clips. With a bayonet forceps, the tumor was found to be more or less cystic, free anteriorly and laterally and adherent posteriorly.

A stab wound was made in the presenting rounded surface of the tumor mass which was found to be about the size and color of a white grape. The contents of the tumor were too gelatinous to flow out, but were carefully scooped out with a curet. Then the entire capsule with some of the remaining substance of the

Fig. 9.—*A*, the flap on the fourteenth postoperative day. *B*, front view of the flap on the day of discharge.

tumor was gently delivered through the foramen by means of a bayonet forceps. A few fine adhesions that held the tumor posteriorly gave way with no bleeding as a result.

In removing cotton wall-offs, a vein anterior to the foramen of Monro was injured, which gave troublesome bleeding necessitating numerous cotton pledgets, irrigation and finally a small piece of muscle to bring it under control. When all bleeding was under control and wall-offs removed, the ventricle was filled with physiologic solution of sodium chloride and the edges of the cortical incision allowed to come together. The dural incisions were closed with interrupted black silk sutures and the flap returned to its former position and closed with interrupted black silk sutures. Throughout the operation, which lasted three hours and twenty minutes, the patient's condition remained good. No change occurred in the motor power of the left side of her face or her left arm or leg during the operation or at any time postoperatively.

Microscopic examination showed about the margins of a large mass of pink homogeneous material a narrow band of tissue thrown up in many papillary folds. The papillae were covered by one or more layers of epithelium lying on a base

of vascular fibrous tissue. For the most part this epithelium was cuboidal and lay on a band of connective tissue fibers. In some zones the epithelium was columnar and ciliated and lay on a base of glial fibers.

The diagnosis was papilloma of mixed ependymal and choroidal origin.

The patient made an uneventful recovery (fig. 9). On May 23, she demonstrated that she could read newspaper print, which she could not do before the operation, and on May 27, she was allowed to sit by her bedside. Contrary to routine instructions in the ward, however, she had been up and walking about on the first, fifth and seventh postoperative days because she wanted to go home or to wait on some nearby patient. On May 31, while eating her breakfast in bed, she became dizzy, fell forward and was unconscious. She said that the bed seemed to be tilting backward and that she felt ill for about fifteen minutes. The bone flap appeared to be elevated. A lumbar puncture was performed. The initial manometric pressure was 280 mm., and after 20 cc. of clear colorless fluid was withdrawn, the pressure was 140 mm. On the following day, the manometric pressure was 60 mm. No further attacks occurred, and the patient was discharged on June 4. She felt very well and showed no mental or neurologic signs. The papilledema had receded so that the outlines of the disks were visible. Follow-up examinations (the most recent one, September, 1933) have shown that the patient remains well.

In these two cases, the tumors of the third ventricle were successfully removed by the same technic. Both were in the anterior part of the third ventricle. In retrospect, it appears to me that a much smaller bone flap would answer every purpose, for only a limited extent of the dural exposure was used in each instance. It does not matter, therefore, how wide a dural exposure is provided since the tumor and its attachment to the third ventricle are just as deeply situated and cannot be drawn to the surface until freed. It is imperative that one work carefully at a distance. Irrespective of the size of the craniotomy, one finds oneself working at a distance from the root, and one has to depend on careful technic to be successful. If the lesion is totally extirpated, a decompression is not required, since the cause of the increased intracranial pressure has been removed.

53 East Sixty-Sixth Street.

SUPRAPERIOSTEAL AND SUBCOSTAL PNEUMONOLYSIS WITH FILLING OF PECTORAL MUSCLES

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Supraperiosteal and subcostal pneumonolysis with a filling of the pectoral muscles may be defined as the freeing of the anterolateral portions of the upper ribs from their periosteum and intercostal muscles and the tucking of the pedicled pectoral muscles between the bared ribs externally and the periosteum, intercostal muscles, pleurae and lung internally.

This procedure is chiefly indicated for cavernous tuberculous or nontuberculous lesions that lie between the clavicle and the level of the third rib anteriorly. The relaxation and rest of the lung that are produced, with or without the aid of hemidiaphragmatic paralysis, tend to check the advance of the pulmonary lesions and to close pulmonary cavities, or to favor the development of fibrous tissue that will do so.

Classic extrapleural pneumonolysis consists in resection of a portion of a rib anteriorly or posteriorly, splitting of the deep periosteum and manual separation of the parietal pleura from the ribs and intercostal muscles. The extrapleural space thus created is then filled with paraffin of 51 C. melting point, masses of fat, gauze, air, rubber dam, an inflatable rubber bag or the pectoral muscles. Each of these "fillings" has its present-day advocates. The direct separation of the parietal pleura from the thoracic wall is a genuinely useful operation. In my experience, paraffin has proved to be the most useful substance for filling, but it has the obvious disadvantages common to any foreign body that is expected to remain in the tissues. Furthermore, stripping of the parietal pleura from the thoracic wall may result in dangerous tearing of the pleura or pleurae and lung, and because of extrapleural inflammatory adhesions it is not always possible to effect separation to the desired extent.

Shivers,[1] Archibald,[2] Goffaerts and de Winther[3] and Sebrechts[4] have been the chief advocates of the use of pectoral muscles to fill an

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From the Department of Surgery, University of Michigan.

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3. Goffaerts and de Winther: L'apicolyse dans le traitement de la tuberculose pulmonaire, Presse méd. **35**:1301 (Oct. 26) 1927.

4. Sebrechts, in discussion on Bérard and Lardinnois: Traitement chirurgical de la tuberculose pulmonaire, Presse méd. **37**:1334 (Oct. 12) 1929.

extrapleural space such as has just been described. Archibald resects portions of the second, third and fourth ribs anteriorly. Goffaerts and de Winther resect the third rib from the sternum to the "axillary line," and after performing pneumonolysis directly over the parietal pleura they make an incision in the first intercostal space, pull the pectoral muscles through this and arrange and fix them; in a large number of their cases a complicating extrapleural effusion caused them to open the wound widely and to pack it. It must be difficult or impossible to maintain the muscles snugly in position at the limits of the extrapleural space, especially in the dome of the thoracic cavity.

The disadvantages and dangers of creating for the pectoral muscles a space that lies directly on the parietal pleura prompted me more than six years ago to devise the operation that is the subject of this article.

The indications for it are, broadly, those that govern the use of paraffin in extrapleural pneumonolysis. Such simple measures as a fair trial of the regimen at the sanatorium, induced pneumothorax and perhaps interruption of the phrenic nerve together with scaleniectomy should be undertaken before pneumonolysis is resorted to. The pulmonary cavity to be closed should be in the upper part of the lung and be small or medium-sized, because extrapleural pneumonolysis rarely closes a large cavity, but tends to displace it downward. The majority of the infiltrative lesions should likewise be limited to the upper part of the lung. These conditions being fulfilled, the greatest value of pneumonolysis is for those cases of tuberculosis in which active disease in the opposite lung contraindicates even partial thoracoplasty. An occasional indication exists for patients with a small chronic cavity in whom there is no contraindication to thoracoplasty but in whom pneumonolysis appears to be a safer operation than thoracoplasty. The safety and effectiveness of the modern many-stage extensive thoracoplasty make a partial or complete thoracoplasty almost always the preferable operation, provided that there is no direct contraindication to it.

The use of supraperiosteal pectoral pneumonolysis is unfortunately limited by certain conditions that do not limit the classic operation of pneumonolysis. It is not applicable to cavities that extend above the level of the clavicle or to cavities that lie posteriorly rather than anterolaterally. The volume of the pectoral muscles must be sufficient to relax the diseased lung to the requisite extent, even though some atrophy may occur from pressure and disuse in spite of maintenance of the muscles' principal nervous and blood vascular supply. The introduction at one operation of a sufficient volume of muscle to close the pulmonary cavity is dangerous to a cardiocirculatory system the func-

tional reserve of which is insufficient to endure the sudden increase of intrathoracic pressure. This disadvantage is common to thoracoplasty performed in too few stages and to all fillings that are used with extrapleural pneumonolysis, with the exception of gauze, crumpled rubber dam and rubber bags, the volume of which may be gradually increased, but at the cost of an open wound. In five of my seven patients on whom pectoral pneumonolysis was performed there was surprisingly little immediate or delayed reaction to the operation. In one patient, who was a poor risk from the cardiocirculatory standpoint, the pulse was irregular for one day after operation and then became normal. One patient died, presumably as the result of pressure on her mediastinum. It would appear to be wise to use less than the entire pectoralis major as a filling if it is abnormally voluminous and if there is doubt about the patient's cardiocirculatory reserve.

It is obvious from the number of restrictions that are placed on the indications for supraperiosteal pectoral pneumonolysis that relatively few patients present suitable conditions for it. Since I first used it on May 12, 1927, I have performed the operation on only seven patients among eleven or twelve hundred who have been operated on for tuberculous or nontuberculous suppurative pulmonary disease. The operation is, however, sufficiently valuable for the occasional patient to justify its being reported.

Its chief advantages are: 1. It is simpler than other methods of using the pectoral muscles as a filling after pneumonolysis. 2. The lung may be freed from the ribs as widely as desired, and its collapse is therefore not dependent on the absence of tough extrapleural adhesions, which not rarely prevent an adequate pulmonary collapse in extrapleural pneumonolysis. 3. There is virtually no danger of wounding the pleura and lung, as the pleura is not even exposed. The operation may, therefore, be safely used in the presence of partial pneumothorax. 4. As no rib is resected, the filling is efficiently retained, and the expectorating mechanism, which is important in the prevention of stasis pneumonia, is but little interfered with. 5. The periosteum of the bared ribs is pushed deep into the thorax and presumably forms new ribs within approximately six weeks, which tend to maintain the lung in the collapsed position even though the muscles atrophy.

Lilienthal [5] has used temporary supraperiosteal packing after resection of ribs. Felix Miller [6] and Haight, Harvey and Oughterson [7] have

5. Lilienthal, Howard: Tuberculosis of the Lungs: Apicolysis by Two Different Methods, S. Clin. North America **8**:235 (April) 1928.

6. Miller, Felix: Presentation Before the Texas Surgical Society, Feb. 3, 1930, Collected Proceedings of the Texas Surgical Society, to be published.

7. Haight, Cameron; Harvey, S. C., and Oughterson, A. W.: Surgical Treatment of Peripheral Lung Abscess: Extrapleural Compression with a Rubber Bag, Yale J. Biol. & Med. **3**:235 (Jan.) 1931.

used the principle of my technic but substituted an inflatable rubber bag for the pectoral muscles as a filling.

OPERATIVE TECHNIC

The operation is performed under gas anesthesia with the patient in about a 15 degree Trendelenburg position. This aids the pulmonary secretions to gravitate toward the mouth and lessens the chance of their entering uninfected portions of the lungs. The incision, indicated in figure 1, is made to the pectoral fascia, and the skin and subcutaneous fat are then lifted from the entire surface of the pec-

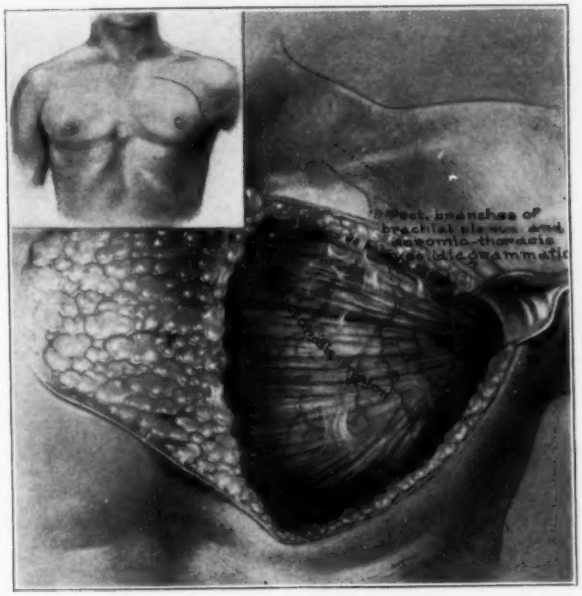

Fig. 1.—Cutaneous incision. The position of chief nerves and vessels (acromiothoracic axis) of the pectoral muscles is indicated.

toralis major muscle. The costal and sternal, but not the clavicular, portions of the pectoralis major are then separated from their origins, and the humeral tendon is divided near the bone. The pectoralis minor is then separated from its ribs of origin; its insertion into the coracoid need not be divided. Care is taken that the principal neurovascular supply of the muscles (the external and internal anterior thoracic nerves and the pectoral branches of the acromiothoracic axis) is not injured because on its integrity as a pedicle depend the viability of the large muscular mass and its protection against rapid atrophy.

The pedicle pectoral muscles are turned upward (fig. 2) and protected with a warm moist cloth. Next, the periosteum is stripped from the anterolateral portion of those ribs that overlie the cavity and its neighboring lung. In three cases this included the second and third ribs and the inferior edge and posterior surface of

Fig. 2.—All of the pectoralis major, except its clavicular fibers, has been detached from the thoracic wall and humerus. The pectoralis minor has been detached from the ribs but not from the coracoid process. The chief neurovascular pedicle of both muscles is intact. Parts of the upper three ribs have been freed from their periosteum. The periosteum, the intercostal muscles and the underlying lung have been retracted from the bare ribs.

Fig. 3.—The pectoralis minor has been tucked into the first intercostal space and tacked in place under the first rib.

the first rib (fig. 2). In one case it included also the fourth rib; in another case only the second, third and fourth ribs were freed, and in two cases only the first and second ribs. Separation of the periosteum of the first rib is facilitated by having the arm well abducted; care must be taken not to injure the first portion of the axillary vein. The portions of the ribs that have been freed from their periosteum undergo gradual atrophy (fig. 5), but in none of my cases have they necrosed and sequestrated.

One of the chief limitations of this operation is that it is indicated only for cavities that do not extend above the clavicle, because separation of the lung and pleurae together with a protecting layer of soft tissues is not possible above the superior edge of the first rib. If an extrapleural space were to be created between

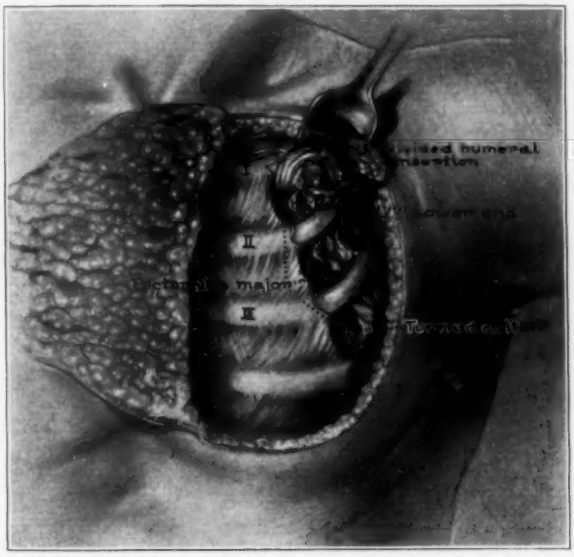

Fig. 4.—The pectoralis major was pulled through the first intercostal space, downward beneath the second and third ribs and out through the third intercostal space. Its deep surface was then stitched to the periosteum of the fourth rib and the redundant muscle pulled upward beneath the third and second ribs and stitched to itself in the first intercostal space. A drain for serum was placed dependently in the axilla.

the first rib and the dome of the thorax, the periosteum of the first rib would need to be divided and separation of the lung and pleura from the thoracic wall continued in the endothoracic fascial tissue, as in the classic type of extrapleural pneumonolysis. This combination of the two types of operation is probably feasible, but I have not yet used it.

After the anterolateral portions of the first, second and third ribs have been freed from their periosteum, the periosteum and intercostal muscles between the fourth rib and the superior edge of the first rib fall far away from the bare ribs. Obviously, the volume of the underlying lung is reduced, and the walls of the contained cavity, if not too rigid, approach one another.

The next step in the operation is to tuck the pectoralis minor into the first intercostal space and between the first rib and its separated periosteum, and to tack it in place with one or two sutures between it and the unseparated periosteum laterally on the lower edge of the first rib (fig. 3).

The lower edge of the pectoralis major is seized by two hemostats which have been passed upward, deep to the bared ribs, and gently drawn backward by means of a wiggling motion of the hemostats through the first intercostal space, then downward behind the bared ribs and in front of the insunken periosteum and intercostal muscles, and finally forward through the third intercostal space. The deep surface of the muscle is tacked with a few catgut sutures to the periosteum of the upper edge of the fourth rib, and the edge of the muscle is again seized by hemostats, this time introduced from above, and is drawn upward just behind the third and second ribs to the first intercostal space, where it is tacked to itself (fig. 4).

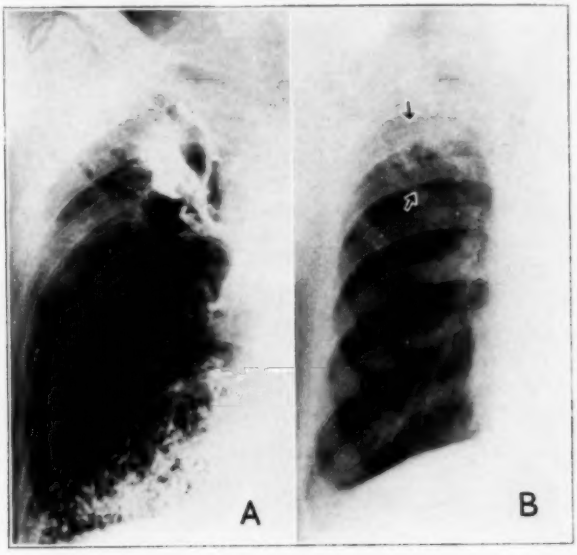

Fig. 5.—*A*, a nineteen month old nontuberculous abscess, filled with iodized oil, in a 53 year old man; 120 cc. of foul sputum was expectorated. The onset was gradual, probably secondary to a diseased mouth. Induced pneumothorax was unsatisfactory. *B*, the area three years after supraperiosteal pectoral pneumonolysis. There was no sputum or symptoms. The upper arrow indicates the spur of the regenerated periosteum. The lower arrow points to marked atrophy of the second rib; the third rib is atrophied to a less extent.

Beneath the anterolateral portions of the upper three ribs there are now the pectoralis minor and a double thickness of the pectoralis major muscles.

Wiggling the pectoralis major through the first intercostal space caused a fracture of the atrophic second rib in the case of a 56 year old man; this made no apparent difference in the postoperative course.

A stab incision is made in the posterior cutaneous flap for serum drainage of thirty-six hours' duration, and the cutaneous incision is closed. A snug pressure dressing is applied. In none of the seven patients has there been any infection of the wound.

The postoperative care is the same as after a radical resection of the breast, and the ultimate function of the arm is the same (fig. 7).

The sudden reduction in volume of the diseased lung causes its secretions to flood the bronchi, and it is therefore important that the patient expectorate as completely as possible as soon as he awakens on the operating table from the gas anesthesia, and that he continue to expectorate freely during the postoperative period. Immediately before operation he should have coughed up all loose sputum.

Seven patients have been operated on by this technic. One, a man of 53 with arteriosclerosis, had a foul nontuberculous abscess (fig. 5) of nineteen months' duration, twelve months of which he spent in a sanatorium. After operation improvement was rapid at first, then gradual; three years after operation the patient had no sputum and was apparently cured. On three of the six tuberculous patients the operation was intentionally done preliminary to thoracoplasty in order to displace

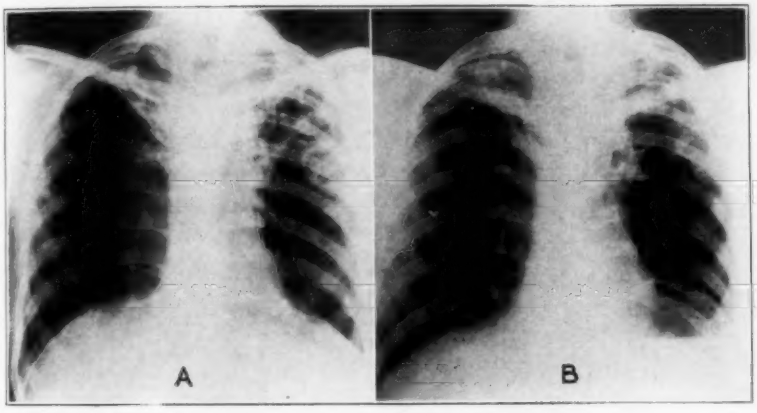

Fig. 6.—*A*, bilateral tuberculosis of seven years' duration in a 24 year old man. There was marked loss of weight, and 150 cc. of sputum positive for tubercle bacilli was expectorated. On the left side there is a chain of four cavities between the first and fourth ribs anterolaterally. The patient had failed to benefit markedly from several residences in sanatoriums. Pneumothorax could not be induced because of adhesions. Thoracoplasty was contraindicated because of active tuberculosis in the right lung. *B*, seven months after supraperiosteal pectoral pneumonolysis no cavity was visible. Within six months after the operation the patient had gained 35 pounds and during the last four months his sputum had been repeatedly negative for tubercle bacilli.

a large cavity backward so that the thoracoplasty would have a better chance of completely closing it; this expectation was apparently met in all three. The extensive and effective thoracoplasty that is used at present would rarely need the preliminary aid of pneumonolysis.

One of the three remaining patients, for whom the operation was used independently, died as a result of the operation, which was the third death in the whole series of seven operations. The patient was

27 years old; he was fat, was losing weight and had persistent night sweats. On anatomic grounds, a thoracoplasty was indicated but was feared because of doubt about a "fatty heart." Immediately before pneumonolysis, the blood pressure was 104 systolic and 80 diastolic; the pulse rate, 78, and the respiratory rate, 24. Immediately after operation, the blood pressure was 114 systolic and 82 diastolic; the pulse rate, from 126 to 134, and the respiratory rate, 42. The pulse continued to increase in rate and became of poor quality. Five hours after operation the pectoral muscles were removed from beneath the ribs, but without

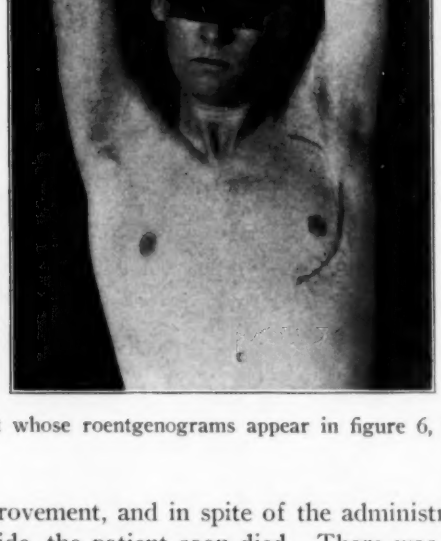

Fig. 7.—Patient whose roentgenograms appear in figure 6, three months after operation.

causing any improvement, and in spite of the administration of oxygen and carbon dioxide, the patient soon died. There was no necropsy.

Another patient for whom the operation was used independently was 56 years old and had arteriosclerosis, intestinal tuberculosis and an anal fistula, dyspnea, hemoptyses, fever and a rapid pulse. He expectorated from 150 to 210 cc. of sputum daily and had had pulmonary tuberculosis for two and a half years. When discharged from the sanatorium seven months after operation, he had gained 20 pounds (9 Kg.), and a roentgenogram showed great clearing in the tuberculous infiltration and apparent disappearance of the cavity; the sputum, however, had been reduced only to 70 cc. daily and was still positive for tubercle bacilli.

The last patient (figs. 6 and 7), 24 years old, had had pulmonary tuberculosis for seven years and had been in sanatoriums on several occasions. He had lost much weight and had expectorated 150 cc. of sputum daily that was positive for tubercle bacilli. Thirteen months after operation he had gained 35 pounds (15.9 Kg.); his sputum was reduced to 10 cc. daily and was repeatedly negative for tubercle bacilli during the last four months. This patient presented ideal indications for the operation. Pneumothorax could not be induced because of pleural adhesions. Phrenicectomy alone would almost certainly have been insufficient. Thoracoplasty was contraindicated because of active tuberculosis in the opposite lung. Extrapleural pneumonolysis with paraffin would have been dangerous because the cavities were close to the parietal pleura.

Churchill [8] used supraperiosteal pectoral pneumonolysis for three patients. The results were at first satisfactory but later "not brilliant," probably, he thought, because of muscular atrophy.

SUMMARY

1. Supraperiosteal and subcostal pneumonolysis with a filling of the pectoral muscles is the freeing of the anterolateral portions of the upper ribs from their periosteum and intercostal muscles and the tucking of the pedicled pectoral muscles between the bared ribs externally and the periosteum, intercostal muscles, pleurae and lung internally.

2. The operation is a form of collapse therapy for cavernous tuberculous or nontuberculous pulmonary suppuration. Its indications are much the same as those of the classic extrapleural pneumonolysis, with certain restrictions imposed by the nature of the operation. The indications are relatively few.

3. The supraperiosteal and subcostal placement of the pectoral muscles has important advantages over their placement in a space directly next to the parietal pleura: It is simpler; one runs no risk of tearing the pleurae and lung; the extent of the pulmonary collapse to be produced is readily controllable and is not dependent on the absence of tough extrapleural adhesions; as no rib is resected, the expectorating mechanism is but little interfered with and so the danger of stasis pneumonia is small; the periosteum of the bared ribs is pushed deep into the thorax where it may be expected to form new ribs that will prevent expansion of the lung when the pectoral muscles atrophy.

4. The operative technic is described, and experiences (including Churchill's) with ten cases are given.

8. Churchill, E. D.: The Selection of the Operation for the Patient in Pulmonary Tuberculosis, New England J. Med. **205**:519 (Sept. 10) 1931.

DIURNAL INCONTINENCE IN WOMEN

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There is a type of urinary incontinence in women, termed diurnal incontinence, which usually follows the trauma of childbirth, but which presents no visible injury or infection of the bladder, and has no relation to vesical fistulas. The onset is slow and insidious, the patient rarely being able to determine a definite beginning. The first symptom is the escape of a few drops of urine when the patient coughs, sneezes or makes any sudden movement which increases abdominal pressure. The condition may progress slowly until a continuous leak is present, although occasionally it remains constant; in fact, its limits vary between a slight dribbling on exertion to continuous loss, even when the patient is recumbent. Few infirmities are productive of so much inconvenience, discomfort and mental depression, nor does any other physical disability interfere so completely with the present comfort or future prospects of its victims.

It has always seemed strange that a symptom so distressing as diurnal incontinence should not be mentioned when it is present. However, in older women, especially when the incontinence is only slight, the condition is often ignored, unless specifically asked about. Watson has commented on the absence of complaint of this condition. In 63 cases with cystocele, some degree of incontinence of urine was mentioned in only 19 histories, but when questionnaires were forwarded, 41 additional complaints were obtained. In 183 cases with cystocele, Watson [1] noted urinary incontinence in 120 or 66.1 per cent after detailed questioning concerning this specific symptom. Taylor [2] has even gone so far as to have definite questions regarding incontinence of urine printed in the histories.

Diurnal incontinence should not be confused with frequency of urination, in which there is no wetting of the clothes from urinary dribbling or leakage, but increased frequency in the desire to urinate. Urgency of urination is also different from incontinence or frequency. When the desire to urinate comes, it must be satisfied, even though on

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From the Department of Gynecology, School of Medicine, Tulane University.

1. Watson, B. P.: Imperfect Urinary Control Following Childbirth, and Its Surgical Treatment, Brit. M. J. **2**:566, 1924.

2. Taylor, H. C., and Watt, C. H.: Incontinence of Urine in Women, Surg., Gynec. & Obst. **24**:296, 1917.

some occasions the clothes can scarcely be removed in time. Urgent urination often occurs in a normal bladder which is greatly distended, or, as is well known, it may result from a mental association with urination, running water, etc. With increased frequency and urgency, there is always first the desire to urinate, while in incontinence the urine passes without any inclination to urinate or even against voluntary effort to control it. It is well described as a "leaky bladder."

OCCURRENCE

Diurnal incontinence, although it has been observed in nulliparous women, is most common in parous women over 40 years of age (Kelly [3]), and the degree of incontinence is, in general, dependent on the number of children. Taylor and Watt [2] offer the following figures showing its association with an increase in the number of children: 8 per cent with no children, 14 per cent with from 1 to 3 children, 25 per cent with from 4 to 6 children and 29 per cent with from 7 to 9 children.

In some women this condition develops, however, when there is no surgical or obstetric history. It may appear immediately after confinement with instrumental delivery; if it does, as it did in 3 of my cases, rest in bed, hot vaginal douches, daily irrigations of the bladder and the maintenance of an empty bladder, by either frequent catheterizations or an indwelling catheter, will usually result in restoration of normal urinary control.

Contrary to the current belief, diurnal incontinence is not always associated with the more obvious forms of genital displacements, cystocele or prolapse. In fact, in prolapse the retention of urine, the opposite of incontinence, is more often observed. Occasionally the patient actually has to push the cervix upward before she can urinate. The type of incontinence in prolapse, caused by the overflow of retention of urine, has a purely mechanical etiology. Often on superficial examination the vagina, urethra and bladder grossly appear normal. However, if the patient takes a squatting position, and coughs, the typical displacement of the urethra and bladder will take place, which, as described by Bonney,[4] appears as a wheeling of these organs around and under the subpubic angle, until, at the height of the movement, the urethral meatus is directed upward and forward. Bonney claims that it is at this degree of displacement of these organs that the spurt of urine occurs.

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3. Kelly, H. A., and Dumm, W. M.: Incontinence in Women Without Manifest Injury to the Bladder, Surg., Gynec. & Obst. **18**:44, 1914.

4. Bonney, V.: Diurnal Incontinence of Urine in Women, J. Obst. & Gynaec. Brit. Emp. **30**:358, 1923.

DIAGNOSIS

Diagnosis is not always easy. It must be remembered that urinary control in women is less certain than in men. Even with actual evidence of wet clothes, one is often impressed with the difficulty to determine whether the relaxation is due to disturbance of the nerve control to the sphincters, to weakness of the muscles or to their injury. In the nulliparous woman who has never had an operation, it must be assumed that the incontinence is the result of nerve disturbance or of progressive muscular weakness. When passing a catheter or instrument into the bladder, one is often impressed with the lack of sphincteric resistance. This does not necessarily mean lack of sphincteric control, since there exists only a narrow line between a sphincter which will hold water and one which is practically worthless. The slow withdrawal of the Pezzer catheter, until it hangs at the neck of the bladder, is probably the best means of locating the sphincter, while the sound is more convenient to identify an associated cystocele or prolapse.

The endoscope offers a visual method of watching the function of the sphincter while the patient is in the knee-chest position and the bladder is distended with water or air. It will be observed that on withdrawing the endoscope, the vesical sphincter closes over the end of the instrument with its normal tonicity. In diurnal incontinence prompt contraction of the sphincter is not generally observed.

Urinary fistulas, aberrant ureters, cystitis, tabes dorsalis, urethritis, trigonitis, spina bifida, and lesions of the central nervous system must be ruled out as the source of any organic factor in the etiology of diurnal incontinence.

EXPERIMENTATION

Bonney[4] performed the only experimental work in testing the strength of the vesical sphincter or the expulsive power of the bladder that was found described in the literature. Measuring the force exerted with a water manometer attached to a catheter inserted in a partly filled bladder, he told the patient to attempt urination and then to cough. In 6 patients there was marked variation, from 100 to 8 mg. of mercury, in the force exerted, while coughing produced only an additional rise of 12 mg. in the 3 patients examined. The catheter was again introduced only as far as the external urethral meatus of an empty bladder, while the water head pressure was raised to sufficient force to overcome the sphincteric contraction and pass into the bladder. In 5 of the 6 patients examined in sitting positions the expulsive force of the bladder was greater than the pressure required to dilate the sphincter from below. In general, Bonney's conclusions were that the escape of urine on coughing in diurnal incontinence is not, or is only partially, due to the intra-

vesical pressure overcoming the sphincter muscle; it is due rather to some interference with the intrinsic sphincteric mechanism. He suggests, however, that his experiments are too few to allow him to dogmatize.

ANATOMY

General anatomic descriptions of the bladder vary between excess of detail, which is monotonous and confusing, and broad statements, which tend toward anatomic inaccuracy. For the sake of clarity, the anatomy of the female bladder is outlined under three headings: the bladder proper, the vesical supports and the sphincteric control of the bladder. The bladder can be described as having a mobile portion, its wall, which distends and contracts according to the contents, and a fixed or immobile part, the trigone, which represents a place of entrance of the ureters, of exit of the urethra and of juncture of the muscle walls of the bladder looping around the vesicle neck and upper part of the urethra. It is only this fixed part, the trigone and base of the bladder, with which I am concerned, since, as I shall attempt to show, any relaxation or weakness of this part will give rise to the type of incontinence under discussion.

The most anterior portion of the bladder and trigone rests on a deep facial sheath which is attached to the posterior aspect of the pubic bone and to the under surface of the fascia of the rectus and pyramidalis muscles. If this union is divided when a low, midline incision is made, the bladder tends to fall backward, and because of this I make it a point, after this type of incision, to anchor, by a special stitch, the bladder and its peritoneal fold to its original attachment. This sheath runs posteriorly in a horizontal manner, then angulates itself upward to be attached to the cervix. The lateral attachment of this sheathlike structure is the levator ani muscles and the parametric tissues. Hence it is readily seen that the vesical trigone is strongly attached anteriorly, and thus assures itself of excellent support, while posteriorly the angulated part of the fibromuscular sheath is weak, and its attachment to the cervix, a movable organ, does not assure this posterior part of the trigone and urethra the same support of fixation as noted anteriorly. I stress the weakness of the trigone posteriorly and its strength anteriorly as the main source of diurnal incontinence. The fascial planes of cleavage of this sheath are made use of when the bladder is separated from the anterior vaginal structures in the performance of an abdominal panhysterectomy and in vaginal operations requiring separation of the bladder from the anterior vaginal wall.

It is believed that there are two urinary sphincters in a woman, the vesical and the urethral. The former is composed of the smooth muscles of the bladder wall, as shown by the blending of the bladder mucosa with the vesical structures. Its control is involuntary. However, there

is some doubt as to its real existence and functions, as has been shown by dissection (Grimsdale). The urethral sphincter, the external sphincter, composed of striped or voluntarily controlled muscle, is formed of the circulatory fibers of the perineal muscles lying in the musculofascial sheath already described, and is closely associated with the fibers of the urethral compressor muscle. In fact, nowhere along the urethral tract are the walls of the urethra thicker than they are at this location, being situated between the fascial planes which support the trigone. It is a distinct muscular structure, and since it is so firmly embedded in the fixed trigonal supports arising from the pubis, I feel that its sphincteric powers are one of the main controls of the act of micturition, and that its proper functioning will prevent diurnal incontinence.

The nerve supply to the bladder is from two sources: 1. The fibers of the second, third and fourth sacral roots maintain voluntary control. 2. These fibers mingle with the sympathetic innervation in the superior and inferior hypogastric plexuses, which is the source of involuntary vesical control; the nerve fibers from both sources descend along the ureters and vesical blood vessels to reach their destination.

MICTURITION REFLEX

Before investigating the sphincteric mechanism in diurnal incontinence, the normal physiology of urination and the micturition reflex should be examined, since I consider micturition such a complex act that any fault in its mechanics might be more important than an anatomic defect. The act of micturition is performed through the reciprocal stimulation and inhibition of the vesical sphincters and the bladder musculature, aided by voluntary increase of intra-abdominal pressure. That there is a voluntary and involuntary control over emptying the bladder is attested not only in the conscious and unconscious states of being, but also by the infant's reflex response to its first desire to urinate. Later these first demands to urinate are resisted through voluntary control through the higher nerve centers. Some recent work suggests an intrinsic or automatic nerve mechanism within the bladder walls.

I should like to stress the complexity of this reflex of micturition. No matter what might be the causative mechanism at the onset of micturition, once urine begins to pass the sphincteric levels, the immediate cessation of urination is difficult, since the sphincteric control is reflexly inhibited. In this difficulty lies a possible explanation of the unpleasant wetting of the clothes in diurnal incontinence.

MECHANISM

Many theories of the mechanism causing diurnal incontinence are offered. One example is Bonney's [4] description of the laxity of the

anterior part of the musculofascial sheath, so that it yields to sudden pressure and allows the bladder to slip behind the symphysis pubis and the urethra to fall downward and forward by wheeling round under the pubic arc. Bonney, however, offers no explanation of a similar displacement of these organs without incontinence. I cannot agree with Bonney's idea of the existence of a valvular mechanism at the angle of the movable bladder and fixed urethra; no similar mechanical arrangement is found at the orifice of any other meatus when relaxation occurs.

Young [5] is of the opinion that no incontinence can exist as long as the external or voluntary sphincter is intact, and that incontinence can occur, as noted by this author, only when sphincteric power is lost. Dougal [6] supports Young's theory and adds evidence to this hypothesis by noting the maintenance of urinary control in prolapse. Watson [1] conforms to a similar belief of the importance of the external sphincteric control. Stoeckel may be correct in emphasizing the importance of obstetric lacerations to the internal sphincter, with resulting restricting adhesions, but the importance of this is doubtful because of the indifferent sphincteric findings on the cadavers of Grimsdale, and also because obstetric maneuvers tend to elevate and push forward the bladder base under the pubis rather than to tear through it. However, the possibility of damage to innervation of this sphincter from obstetric injuries is not to be overlooked.

I believe that weakness of the natural fixation of the vesical base is an all-important cause in the mechanism of diurnal incontinence. The neck of the bladder and upper part of the urethra are attached anteriorly to the symphysis pubis by comparatively strong fibrous bands, while posteriorly they are incorporated only with the anterior vaginal wall, which is prone to become displaced as a result of obstetric injuries. Relaxation of the inferior neck of the bladder and posterior urethra drags on the anterior vesical supports and forms a type of suspensory ligament which causes a funnel-shaped orifice to occur at the internal urethral meatus. With such a funnel-shaped relaxation of the internal sphincter (ready to pass urine) and with the associated complex micturition reflex (when once urine is allowed to pass the urethral sphincter more urine flows freely), it is easy to conceive that incontinence would be the result of sudden abdominal strain, even though no cystocele were present. When the latter condition exists, even in the absence of incontinence, the musculofascial sheath retains its tension in the region of the

5. Young, E. L.: Urinary Incontinence in the Female, J. A. M. A. **79**:1753 (Nov. 18) 1922.

6. Dougal, D.: Urinary Incontinence in Women, with Special Reference to the Operative Treatment in Young Nulliparae, J. Obst. & Gynaec. Brit. Emp. **31**: 46, 1924.

neck of the bladder and urethra, both posteriorly and anteriorly, but it is weakened over that portion of itself which is angulated on the anterior vaginal wall and which ultimately is inserted into the cervix. I contend, therefore, that the damage causing incontinence alone and that causing cystocele alone occur at different places. The former is definitely associated with weakness of the posterior aspect of the neck of the bladder and the urethra, with the anterior attachments to the pubis remaining intact and thus supporting the base of the bladder by the anterior wall of the sphincter; while true cystocele is a bladder hernia, protruding between the edges of the separated fascial layer

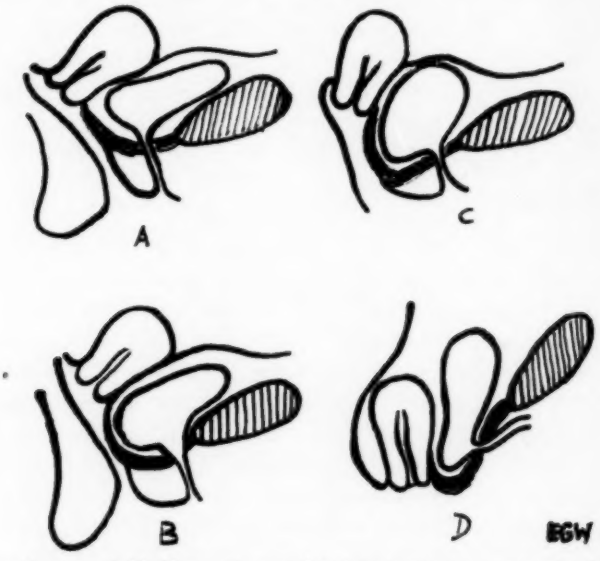

Fig. 1.—*A*, normal bladder. *B*, associated incontinence; note the funnel-shaped orifice at the internal urethral meatus. *C*, cystocele; the bladder is torn from its pubic attachment and sags posteriorly, but there is no drag on the urethra. *D*, prolapse; the part of the bladder below the urethra often retains urine after voiding.

supports, and therefore not necessarily associated with damage of the sphincter.

In addition to the sphincteric weakness, I consider the tonicity and strength of the vaginal walls as important factors in the production of diurnal incontinence. Complete relaxation of the posterior and anterior vaginal walls will eventually result in procidentia, while relaxation of these walls in various degrees usually gives rise to rectocele or cystocele alone or in combination. If, however, only the anterior wall is weakened from obstetric injuries, and the pelvic floor maintains its normal support, the cervix will push downward in a piston fashion if there is a sudden increase of abdominal tension. The only outlet for such a

force is on the weakened anterior vaginal wall, tending to drag the posterior aspect of the base of the bladder and the urethral neck with it, since the perineal floor posteriorly maintains sufficient strength to direct forward and anteriorly the plunging action of the cervix.

That such obstetric injuries can occur only to the anterior vaginal wall, while the perineal floor remains comparatively normal, is often seen in the narrowed angle type of pelvis, in which episiotomy is common and too frequently the oncoming head is pushed forward to "save the perineal floor." Also, the long tedious labors of women with this type of pelvis, compared to the easy delivery of women with a broad-angled pelvis, tend to increase injuries to the anterior vaginal wall. Watson [1] suggested early prophylactic episiotomies in the narrowed arch pelves as preventatives to subsequent diurnal incontinence.

Van Duzen [7] dissected the trigonal and urethral tracts of cadavers. He found that injuries to the trigonal muscle and separation of it from the underlying fascial sheaths posteriorly produce cystocele. He obtained several bladders from women who died shortly after their first delivery, and in all those examined there was only partial division of the interureteric muscle, whereas in cadavers of multiparous women, the entire trigonal muscle was often atrophied, attenuated or even absent. In cadavers of younger women this important muscle was partially destroyed in all cases after a sufficient lapse of time since the last delivery. His natural conclusions were that repair work from obstetric injuries on the anterior vaginal wall should be performed as early as possible.

Undoubtedly, local pelvic injury at the time of parturition is considered the most important single cause of this deplorable condition, and, because of the unfortunate results following delayed repairs after confinement, I strongly advocate immediate operation on the posterior vaginal wall and repair of the anterior wall as soon as involution has taken place. In fact, this is a point that one cannot overemphasize. Too often I have seen complete tears into the rectum or vesical-vaginal fistulas develop from only partial damage to these parts; but if infection sets in untoward results usually follow, or else the irregular scar formation gives rise to local pelvic pain or often to abnormal functioning of the organs involved.

TREATMENT

As stated by Young,[5] "The records of attempts to cure urinary incontinence in the female are interesting illustrations of the inability of most men to go straight to the point in working on any problem involving a part of the human body." The history of the various

7. Van Duzen, R. E.: The Use of the Cystoscope as a Control in the Diagnosis and Treatment of Cystoceles, Urol. & Cutan. Rev. **36**:187, 1932.

phases of treatment offers many methods, of which the majority are more or less futile, many ridiculous, and some even dangerous. Contractile collodion has been painted over the internal meatus, radical cauterization of the urethra has been used, and even paraffin has been injected under the mucosa to insure permanent pressure around the lumen of the urethra. Silk stitches have been placed around the urethra to form an artificial sphincter. Hydrotherapy, in the form of hot or cold footbaths and douches, has proved of no avail. Lumbar puncture and injections into the sacral nerve roots have been tried in the hope of stimulating sphincteric action. Tampons and pessaries locally placed have always failed, as have drugs. Pressure bandages, dieting, hygienic measures, counterirritants by means of blister formation and electricity have been employed. Permanent artificial channels to the bladder have been opened from various locations. Advancement of the urethra, by a method described by Pawlick and improved by Dudley, resulted in 4 of 5 cures by the latter author. Frank described partial resection of the urethral wall to lessen the circumference of the lumen, while Gersuny, Pousson and Ries have twisted the urethra and then resutured it in its original location. Transplantation of muscles to form new sphincters has been devised; Goebel's technic, improved by Stoeckel, makes use of strips of muscle from the pyramidalis, bringing them downward posterior to the symphysis. Taussig [8] has employed the levator ani muscles, Deming [9] the gracilis and Novwy the adductor magnus and biceps femoris to perform the same function. H. H. Young [10] employs both the suprapubic and the perineal approaches in males, but I am inclined to believe that suprapubic drainage should be reserved for cases in which the vaginal route is technically too difficult, that is, when the vagina is very small, senile or atrophic, as scar tissue is often present around the base of the bladder.

In 1914 Kelly reported 20 cases with 16 cures in which the neck of the bladder was plicated with a mattress suture of fine linen. Since this report, other gynecologists have employed Kelly's technic with minor variations. E. L. Young [5] advocated the isolation by dissection of the torn external ends of the sphincter, and their resuture; plication of the vesical neck is thought to be only secondary in importance. He cured 18 patients, 100 per cent, by this technic. He described the ease with which these torn ends of the sphincter can be isolated and

8. Taussig, F. J.: A New Operation for Urinary Incontinence in Woman by Transposing Levator Ani Muscles, Am. J. Obst. & Gynec. **77**:881, 1918.

9. Deming, C. L.: Transplantation of Gracilis Muscle for Incontinence of Urine, J. A. M. A. **86**:822 (March 20) 1926.

10. Young, H. H.: Operation for the Cure of Urinary Incontinence, Surg., Gynec. & Obst. **28**:84, 1919.

defined, although in my own experience, I find their isolation next to impossible, and often hesitate to search for them for fear of destroying adjacent tissue which is helpful in sphincteric approximation from fascial support.

Bonney's original treatment, supported by Berkeley, of tautening the vesical sphincter seems rather practical, but now these authorities are of the opinion that the only important consideration is strengthening the anterior portion of the fibromuscular sheath. They consider the overfolding of the periurethral tissue to be far less important at present, since their belief is that true diurnal incontinence is the result of relaxation of the anterior portion of the musculofascial sheath, and, in consequence, the only cure of this malady is the tightening of this weakened support anteriorly.

The operative technic which I have followed is similar to that advocated by Kelly. With the patient in the lithotomy position, an annular

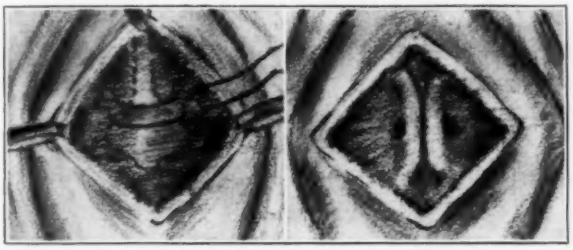

Fig. 2.—Method of insertion of mattress suture at the bladder neck. The first suture is tied.

incision is made around the anterior lip of the cervix at its vaginal junction, and a median incision is carried anteriorly at right angles toward the external urethral orifice. The anterior vaginal structures are separated from the bladder sufficiently posteriorly to expose the bladder base and upper urethral neck, the locations of which can be determined by palpation with the use of a Pezzer catheter inserted in the bladder. By gentle traction on the catheter, and with one finger against the urethral neck, the location of the sphincter is noted as the structure just anterior to the "point of hang" of the catheter on its withdrawal. The actual determination of the location of the external sphincter is essential to insure good postoperative results and to prevent urethral injuries. I do not try, however, to isolate the torn ends of the sphincter, since, as I said before, too much dissection in this region may result in increased destruction of sphincteric tissue, or penetration into the bladder and urethra. I exercise great caution in operating on elderly women whose sphincteric muscle is mainly fibrous tissue, and consequently more

difficult to find and easier to destroy. The aim of the operation is to insert two tiers of mattress sutures so as to include and imbricate on themselves the tissues of, and adjacent to, the neck of the bladder, the sphincter muscle and the posterior urethra, so that these surrounding fibromuscular tissues are enfolded on themselves against the floor of the posterior urethra. In consequence, the urethral lumen is narrowed from side to side at this point. The adjacent tissues are sufficiently secured so that a fixed "point d'appui" is reestablished from which the sphincter can act. Indeed, if one plicates where one thinks the neck of the bladder ought to be, and restores it to its normal location, the resulting cure of incontinence is usually obtained. No undue tension should be made on the sutures, as sloughing may result. An important stitch is the suture on the neck of the bladder to insure additional narrowing of the urethral orifice superior to the sphincter; but the exact location of this suture is not always easy. I make a point of saving as much as possible of the musculofascial sheath, and imbricate it on itself. Only the vaginal mucosal edges are trimmed.

If more extensive injuries, as cystocele, are associated, it is as necessary to repair the sphincteric control as it is to reestablish the normal position of the bladder. Unfortunately, this is a fact frequently neglected and is usually responsible for the persistence of incontinence after the usual type of anterior colporrhaphy.[2] In the combined condition of incontinence and cystocele, in addition to plication of the bladder and urethral neck, I imbricate the remnants of the overlying fascia all the way down to the cervix in order to assure additional vesical support.

The Watkins interposition operation is well chosen in cases of cystocele and prolapse associated with incontinence, in which the senile atrophy of the musculofascial sheath makes its separation from the vaginal mucosa and bladder a difficult procedure. This operation is especially helpful in large, flaccid atonic bladders. A perineorrhaphy in combination with any of the operations mentioned is most important, but such additional support is not always offered. Restoration of all the injured pelvic parts as nearly as possible to their original appearance is the ideal, and so additional support from a repaired pelvic floor tends to relieve part of the strain that otherwise would be borne by the anterior vaginal wall.

Too often the repaired perineum is asked to supply more than its share of support, in fact the whole support, and I cannot condemn too strongly the simple perineorrhaphy, done all too frequently, to cure incontinence. Such operative procedure is only short of a criminal act and has its foundations built on anatomic ignorance, surgical inability and poor judgment.

In associated fibromyomatous growths, any drag by the tumor through the anterior vaginal wall on the sphincteric control should be relieved if the incontinence is expected to be cured.

The effect of subsequent pregnancy and confinement on the permanence of urinary control following incontinence, once it has been established by surgical means, is still an open question, and my experience has been too limited to offer any definite results.

In the rare case in which the operative risk is too great to offer surgical aid, I use a soft ring pessary which I find more helpful than any other procedure. This support is inadequate, but fortunately such cases are rare, and the use of the pessary is correspondingly infrequent.

POSTOPERATIVE CARE

The most important postoperative care is avoidance of infection and overdistention of the bladder. The choice of methods for such treatment is insertion of an indwelling catheter at the time of operation or frequent catheterizations, every six or eight hours postoperatively. I prefer the former, and leave the catheter in place for from six to eight days, since I find less infection and quieter convalescence with this method. After the fifth day, if all is going well, I frequently have the catheter clamped intermittently in order to permit the bladder to accustom itself to its future work, so to speak. It is wise to catheterize the patient after her first normal voiding to insure that there is not too great a residuum of urine, possibly caused by a too snug suture. A small amount of residual urine often occurs, which usually disappears within a week.

Many authorities favor frequent catheterizations over the indwelling catheter. Results reported in the literature do not offer evidence definite enough to substantiate one method in favor of the other. However, I am inclined to feel that the nursing care is an important feature in either method. If the indwelling catheter is allowed to become dirty or plugged so as to obstruct the urinary flow, ideal results are not obtainable; whereas if frequent catheterizations are performed indifferently, so as to stretch the newly sutured sphincteric area, or if they are performed without strict aseptic precautions, untoward results may follow.

CURES

The cures resulting from the different types of operations vary between wide limits; Watson [1] reported 66 per cent cures in 105 cases; Kelly, 80 per cent in 20 cases, Furniss,[11] 80 per cent in 21 cases, and

11. Furniss, H. D.: Urinary Incontinence in Women, S. Clin. North America **5**:249, 1922.

E. L. Young,[5] 100 per cent in 18 cases. My own statistics, based on thirty-four cases of multiparous women, are offered in the following table:

Data in Author's Cases

Age	**Years**
Oldest	65
Average	42.6
Youngest	25
Instrumental deliveries	11 (33%)
Associated cystocele	15 (44%)
Associated rectocele	16 (47%)
Types of operations	
Kelly technic	20
Perineorrhaphy	25
Vaginal hysterectomy	3
Watkin's interposition	2
Repair of complete tear	1
Results	
Cured	14
Improved	5
Unimproved	2
Undetermined	13

CONCLUSIONS

Diurnal incontinence is a most distressing condition, and in view of the fact that the operation advocated for the cure of this discomfort is not difficult, the extent to which its use has been neglected is amazing. Some of the most grateful patients are those who have been helped by operation. In the majority of cases of urinary incontinence, especially in multiparous women, the condition can be cured or, at any rate, relieved by operation. Undoubtedly many single women are allowed to go on suffering from this ailment because no obvious lesion can be found, and the disability is attributed to a neurosis. A neurotic element is present in some cases, especially in the nulliparous girl, in whom urinary control is sensitive to nerve influence; but the real cause usually lies in the weakness of the sphincteric mechanism, which can be dealt with successfully by the surgical methods advocated in this paper.

1640 Arabella Street.

AVULSION OF THE EPIPHYSIS OF THE SMALL TROCHANTER

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Isolated avulsion of the small trochanter is uncommon, only sixty-one cases having been reported in the literature. I have recently observed a case, and wish to report it, in conjunction with the essential facts derived from a study of the sixty-one previously reported cases.

REPORT OF A CASE

History.—A colored boy, aged 14 years, came to the clinic on June 8, 1932, complaining of pain in the upper medial third of the right thigh and stiffness of the right hip. He stated that the day before, during a ball game, he had made a quick stop on approaching a base. As he did this, the trunk was suddenly hyperextended on the lower extremities. He felt something give way in the right thigh; this was accompanied by sharp pain and a fall to the ground. He had to be helped to his feet but found that he could walk unaided by "holding the hip stiff." This could not be accomplished, however, without considerable pain. On reaching home, he immediately went to bed. There was no pain when he was lying quiet with the hip flexed. The following morning he was able to get up and walk to the clinic.

Examination.—Station and Gait: When the patient was standing, the weight was carried mainly on the left leg, the right knee and hip being held in slight flexion. In walking, the right hip was held rigid, and the trunk was bent forward at the hips.

Supine Position: The right hip was held in 30 degrees of flexion. There was no visible swelling, ecchymosis or deformity due to external rotation. There was severe tenderness to pressure over the small trochanter in the upper third of the mesial aspect of the thigh, but there was no shortening of the extremity, and manipulation elicited no crepitus. A full range of flexion and rotation at the hip joint could be elicited passively, if great care was used in the manipulation. The movements of abduction and extension were limited by pain and spasm in the muscles. The patient could actively flex the thigh while lying on his back, but not while seated on the edge of the table with the legs hanging over the side (Ludloff's sign). The clinical diagnosis of avulsion of the small trochanter was confirmed by the roentgenogram (figure).

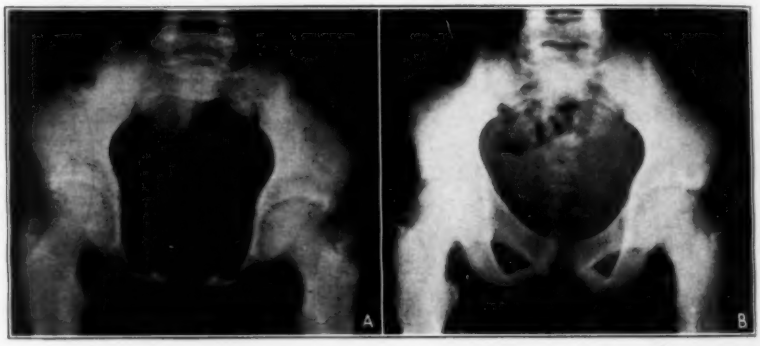
Treatment.—On the day of admission (June 8, 1932) a hip spica was applied, with the affected thigh in a position of 45 degrees of flexion and mild abduction. After three weeks the cast was removed, and brine baths were started. These were given for four days, following which the patient was allowed to walk. There

From the Department of Surgery, University of Michigan.

was a mild limp for a week, but when the patient was last seen (Aug. 18, 1932), nine weeks after the injury, the gait was normal, and the clinical examination showed nothing of note.

ANATOMY

The psoas major muscle arises from the transverse processes and the lateral surfaces of the bodies and disks of the five lumbar vertebrae. The iliacus muscle arises from the iliac crest, from the anterolateral portion of the anterior surface of the sacrum and from the greater portion of the iliac fossa. From these extensive areas of origin the fibers of the two muscles converge downward, forward and lateralward to a small area of insertion on the small trochanter and on the surface of the femur immediately distal to the trochanter. Flexion at the hip joints is produced by the iliopsoas muscles. When the trunk is fixed, contraction



A shows typical upward and medial displacement of the avulsed epiphysis. In *B*, taken five weeks after the accident, the epiphysis is firmly united to the shaft.

of the iliopsoas muscles flexes the thighs, and when the thighs are fixed, their contraction flexes the trunk. The power required to effect these movements is considerable, and hence the pull on the small trochanter must at times be very great.

The center of ossification for the small trochanter appears at about the twelfth year of age and unites with the shaft at about the eighteenth year.

ETIOLOGY AND PATHOLOGY

Predisposing and Immediate Causes.—Isolated fracture of the small trochanter occurs almost exclusively in boys between the ages of 13 and 17 (table 1). The right thigh is almost twice as commonly affected as the left. The fracture often occurs in athletic activities. When a person runs or makes a sudden stop while running, the pull on the epiphysis from contraction of the iliopsoas muscles is so great that the

small trochanter is at times avulsed. The fracture is also often produced as follows: Sometimes, while standing or running, a boy loses his balance, and in order to restore equilibrium, he suddenly hyperextends the trunk on the thighs, thus avulsing the trochanter.

Owing to the depth of the overlying soft tissues, and to the situation of the trochanter on the internal aspect of the upper part of the femur,

TABLE 1.—*Incidence of Avulsion of the Epiphysis of the Small Trochanter*

Sex		Age		Side Affected	
Males	59	Number of cases given	56	Right	33
Females	2	Youngest	8 years	Left	19
Unknown	1	Oldest	87 years	Not given	10
Total	62	Average	19 years	Total	62

Forty-Two of the 56 Patients Were Between 13 and 17 Years of Age, as Follows:

Age	Number of Cases
13	6
14	11
15	11
16	6
17	8
Total	42

TABLE 2.—*Summary of the Methods of Treatment and of the End-Results in 50 Cases*

Number of patients on whom I have data as to the end-results of treatment	50
Number of patients who completely recovered	46
Number of patients who died during treatment	4*
Treatment employed to secure the high percentage of cures (46 of 50 = 92%)	
Traction and rest in bed	5
Rest in bed with sandbags to hold the hip in flexion	14
Hip spica with hip in flexion (varying degrees of abduction or adduction)	19
Operation (wiring epiphysis to shaft)	1
Adhesive strapping	1
Rest in bed only	3
Rest in bed with limb immobilized in flexion in Thomas splint	1
No treatment	2
Total	46

* The four patients who died were: (1) a greatly debilitated man, aged 82, who entered the hospital fourteen days after injury and died on the same day (Juillard, 1879); (2) a boy, aged 19 years, who died of sepsis after receiving some "hard kicks in the buttocks"; autopsy revealed separation of the trochanter (probably pathologic), complicated by infected hematoma and pericarditis (Brunelle, 1854); (3) a boy, aged 17 years, who died of septicemia fourteen days after operation (Fenwick; reported by Hutchinson, according to Ross); (4) a child, aged 8 years, observed by Carthy; the case was cited by Ruhl, but no further details were given.

fracture by direct violence does not occur. For the same reason, the fracture is always a simple one. Several cases produced by indirect force have, however, been recorded. Hoch's [1] patient was struck by a falling chimney piece, while the patients of Naegeli,[2] Peggar,[3] Gray [4]

1. Hoch: Ztschr. f. Chir. **97**:405, 1909.
2. Naegeli: Beitr. z. klin. Chir. **77**:242, 1912.
3. Peggar: Beitr. z. klin. Chir. **81**:138, 1912.
4. Gray: J. Roy. Army M. Corps **18**:578, 1912.

and Heath [5] sustained the fracture by falling with the full weight on the hip.

Pathology.—A large majority of the reported cases of isolated fracture of the small trochanter are in reality cases of epiphyseal separation. The epiphyseal displacement is always in the same direction, upward and medialward, toward the adductor region. In older people, in whom the epiphysis is firmly fused, the trochanter is torn from the shaft, carrying with it a piece of the femoral cortex (six of fifty-nine cases). In such instances the trochanter is occasionally broken into several pieces.

DIAGNOSIS AND TREATMENT

Symptoms and Signs.—When a person is running, suddenly stopping or attempting to restore a lost equilibrium he feels a sharp, severe pain in the upper medial third of the thigh. A feeling of something tearing is not uncommon. The patient often falls to the ground but usually can arise and, by "holding the hip stiff," walk unaided. Some of these patients have been able to walk backward better than forward. As the insertion of the hip-flexor muscle is incompletely torn away, the result is partial or complete disability of the hip-flexor mechanism. There is a loss of ability to flex the thigh actively when the patient is seated on the edge of a table, but when he is lying supine, active flexion of the thigh is possible because of the quadriceps extensor mechanism. This sign (Ludloff) is present in a high percentage of cases and can be considered diagnostic. Flexion deformity of the hip is commonly present, but there is no true shortening, and ordinarily there is no visible ecchymosis. A hematoma is often deeply palpable on the medial aspect of the upper part of the thigh, and tenderness to pressure is marked over the small trochanter. If the thigh is moved slowly and handled gently, the full range of flexion and rotation at the hip joint can be obtained, but abduction and extension are limited by spasm and pain in the muscles.

Differential Diagnosis.—The age of the patient and the absence of deformity due to external rotation, crepitus and shortening serve to differentiate this lesion from fracture of the femoral neck. A contusion of the soft tissues in this region is differentiated by the history of direct trauma, by the presence of a full range of motion in the hip joint and by the absence of the Ludloff sign.

Prognosis and Treatment.—The end-result is given in the histories of fifty of the sixty-one cases reported in the literature. Forty-six of this number are credited with a perfect result. The different methods of treatment employed to obtain this result vary from no treatment

5. Heath, O.: Proc. Roy. Soc. Med. (Sect. Orthop.) **16**:12, 1923.

(two cases) to open reduction (one case), and are listed in table 2. This table shows that the avulsed epiphysis will heal, no matter what form of treatment is used. Even though roentgenograms reveal the fragment considerably displaced, the intervening space between the shaft and the trochanter always fills in with callus, and a perfect union results.

COMMENT

I think that the most logical method of treatment is fixation of the affected thigh in 45 degrees of flexion by a hip spica. This position approximates the fragments and relaxes the iliopsoas muscle. I believe that the cast should extend to just below the knee, with the extremity neutral as to rotation and abduction. After three weeks of immobilization, union is firm and bearing of the full weight may be rapidly accomplished.

SUMMARY

1. Isolated fracture of the minor trochanter is uncommon, my case being the sixty-second to be reported.

2. In practically all cases, it is an avulsion of the epiphysis. It occurs almost exclusively in boys between the ages of 12 and 18, the time during which the epiphysis develops.

3. It might well be termed a "sport injury."

4. Diagnosis can be made on the basis of the history and the physical findings. An important sign is the patient's inability to flex the thigh actively when he is seated on the edge of a table, although there is retention of active flexion when he is supine (Ludloff's sign).

5. The characteristic displacement of the avulsed epiphysis is upward and medialward.

6. Perfect healing with no loss of function was reported in 92 per cent of a series of fifty instances collected from the literature. A wide variety of methods of treatment were used.

7. Treatment consists in three weeks of immobilization of the thigh in flexion, preferably in a plaster cast.

8. No further manipulation or operation is indicated, even though in the roentgenogram the epiphysis appears rather widely separated from the shaft.

INTRAMURAL EXTENSION OF GASTRIC CARCINOMA

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When performing extensive resections for carcinoma of the stomach, one of the most important considerations is to resect clear of the growth.

In this paper it is proposed to show how a general estimate can be made of the probable extension of any given carcinoma into and through the gastric wall. The problem must have presented itself first to Billroth, the originator of resection of the stomach, for Guinard [1] quoted von Eiselsberg as saying that in Billroth's clinic the resected portion extended several centimeters beyond the growth. Mikulicz [2] advocated removal of from 5 to 10 mm. of duodenum and from 5 to 10 cm. of apparently healthy stomach, but in a well defined tumor he thought that removal of from 1 to 2 cm. of apparently healthy stomach was sufficient. Czerny [3] was more moderate, and advocated removal of 3 cm. of apparently healthy tissue. Guinard himself thought that in well circumscribed tumors the resected portion should include 2 or 3 cm. of healthy stomach, but that in the infiltrating type of tumor practically the whole viscus should be removed.

In 1900 Cunéo [4] made the first extensive study of the manner of invasion of the wall by carcinoma of the stomach. He noted that the submucosa is invaded early, that it is invaded to a greater extent than the mucosa, and that at still greater distance from the tumor there are carcinomatous lymphatic structures which cannot be detected except by the microscope. He reported the general tendency of carcinoma of the stomach to spread toward the lesser curvature and to involve the various

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Thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery, November, 1931. Work done while a Fellow in Surgery, the Mayo Foundation, Rochester, Minn.

1. Guinard, U.: La cure chirurgicale du cancer de l'estomac, Paris, G. Steinheil, 1898.

2. Mikulicz, J.: Beiträge zur Technik der Operation des Magencarcinoms, Arch. f. klin. Chir. **57**:523, 1898.

3. Czerny, quoted by Guinard,[1] and by Carle, A., and Fantino, G.: Beiträge zur Pathologie und Therapie des Magens, Arch. f. klin. Chir. **56**:217, 1898.

4. Cunéo, Bernard: Note sur quelques points de l'anatomie pathologique du cancer de l'estomac, Rev. de chir., Paris **21**:513, 1900; De l'envahissement du système lymphatique dans le cancer de l'estomac et de ses conséquences chirurgicales, Paris, G. Steinheil, 1900, p. 34. Cunéo, Bernard, and Delamere, Gabriel: Les lymphatiques de l'estomac (étude anatomique et histologique), J. de l'anat. et physiol. **36**:393, 1900.

groups of lymph nodes. He also recognized that the mucosa of the stomach passed through a polyadenomatous stage to carcinoma; and in this respect, his paper supports the later contentions of MacCarty [5] and of Cheatle.[6]

There is no later paper on the spread of carcinoma in the stomach than that of Cunéo; however, similar studies of the breast have been carried on by Handley [7] and by Cheatle,[6] and on the rectum by Handley,[8] Cheatle [9] and Cole.[10]

I took up the problem in the same manner as Cunéo, and my work was near completion before I read his paper. However, I hope to confirm and to extend his observations. Recent suggestions in regard to the grading of carcinoma and to the manner of its extension in the face of fibrosis and lymphocytosis reveal some interesting facts when applied to a study of the extension of carcinoma of the stomach.

MATERIAL AND METHOD

The fifty specimens used in this study were removed at the Mayo Clinic between January, 1927, and May, 1928. The cases were taken in rotation except when, for some reason, the specimen was unsuitable for study. Certain specimens had been cut so that they were unsuitable, and others had been utilized by fellow investigators. The type of material used can be seen by reference to table 1. The preoperative diagnosis follows: gastric carcinoma, forty cases; gastric ulcer, three; multiple polyps, two; obstructive lesions, two; benign tumor of the stomach, one; deformity of the stomach, one, and pyloric lesion, one.

Each specimen was subjected to the following examination and procedure:

Macroscopic Examination and Description.—The result of this examination will be seen in table 1. The presence or absence of involvement of nodes was noted at this examination, which is the routine adopted in handling all specimens surgically removed at the Mayo Clinic.

Cutting of Block from Tumor on Lesser Curvature.—The blocks were cut from this part of the stomach for two reasons: First, it is in this situation that the surgeon finds most difficulty in obtaining sufficient healthy tissue for his resections, and at this spot the line of resection passes closest to the tumor, and conse-

5. MacCarty, W. C., and Mahle, A. E.: Relation of Differentiation and Lymphocytic Infiltration to Postoperative Longevity in Gastric Carcinoma, J. Lab. & Clin. Med. **6**:473 (June) 1921.

6. Cheatle, G. L.: Desquamative and Dysgenetic Epithelial Hyperplasias in the Breast, Brit. J. Surg. **13**:509 (Jan.) 1926.

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8. Handley, W. S.: Recent Advances in the Surgical Treatment of Some Forms of Cancer, Univ. M. Rec., London **1**:385 (May) 1922.

9. Cheatle, G. L.: The Spread of Cancer in the Lower Part of the Large Intestine, Brit. M. J. **1**:303 (Feb. 7) 1914.

10. Cole, P. P.: The Intramural Spread of Rectal Carcinoma, Brit. M. J. **1**: 431 (March 1) 1913.

TABLE 1.—*Summary of Material*

Case	Description of the Pathologic Condition	Involvement of Lymph Nodes	Plane of Maximal Extension	Classification by Extension	Broders' Grading	Distance of Lateral Extension
1	14 cm. stomach and duodenum; adenocarcinoma (8 by 4 by 1.5 cm.) with nodes inflammatory; endothelial hyperplasia	—	Submucosa	II	2	
2	14 cm. stomach; carcinoma (4 by 5 by 2 cm.)	—	Submucosa	III	4	10 mm.
3	Carcinoma, grade 4 (6 by 6 by 3 cm.) with involvement of serosa	+	Submucosa	IV	4	30 mm.
4	11 cm. stomach; adenocarcinoma (7 by 5 by 2 cm.)	+	Submucosa, serosa	III	3	8 mm.
5	12 cm. stomach; adenocolloid carcinoma (6 by 5 by 1.5 cm.)	+	Submucosa	III	3	No distinct edge
6	13 cm. stomach; adenocarcinoma (4 by 4 by 1 cm.) with one node involved	+	Submucosa	II+	3	No extension
7	13 cm. stomach; small cell carcinoma (9 by 7 by 1.5 cm.)	—	Submucosa	II	4	No extension
8	15 cm. stomach; carcinoma (8 by 7 by 1.5 cm.)	+	Submucosa	III	4	At least 5 mm.; not clear
9	10 cm. stomach; adenocolloid carcinoma (5 by 6 by 2 cm.)	+	Submucosa	II	2	No extension
10	7 cm. stomach; carcinoma (5 by 5 by 1 cm.)	+	Submucosa	II	3	No extension
11	10 cm. stomach; carcinoma (5 by 5 by 3 cm.)	+	Mucosa	II	2	No extension
12	10 cm. stomach; carcinoma (2.5 by 2.5 by 1 cm.); involvement of serosa	—	Submucosa	III	3	6 mm.
13	9 cm. stomach; carcinoma (7 by 4 by 2 cm.); involvement of serosa	+	Submucosa	III	3	11 mm.
14	10 cm. stomach; carcinoma (6 by 6 by 1.5 cm.)	+	Mucosa	IV	4	Not clear; at least 5 mm.
15	10 cm. stomach; adenocolloid carcinoma (3 by 2.5 by 2 cm.) with involvement of serosa	+	Mucosa	IV	4	10 mm.
16	Carcinoma (6 by 5 by 2 cm.); involvement of lymphatic serosa	—	Submucosa	IV	4	5 mm.
17	15 cm. stomach; carcinoma (10 by 7 by 2 cm.) with extensive involvement of nodes	+	Submucosa	III	4	8 mm.
18	13 cm. stomach; adenocarcinoma (8 by 8 by 3 cm.)	+	Serosa	III	3	5 mm.
19	20 cm. adenocarcinoma (8 by 6 by 2 cm.)	+	Submucosa	II	2	No extension
20	15 cm. stomach, 11 cm. of which is small cell, diffuse carcinoma (linitis plastica type) with involvement of serosa	+	All coats	IV	4	Not clear; at least 35 to 40 mm.
21	6 cm. stomach; diffuse carcinoma (linitis plastica type)	..	Mucosa	IV	3	Not clear; no edge
22	13 cm. stomach; carcinomatous ulcer (4 cm. diameter by 5 mm. deep)	—	Submucosa	III	3	10 mm.
23	15 cm. stomach; carcinoma (3 cm. diameter by 12 mm. deep) with involvement of serosa	+	Serosa	III	3	At least 22 mm.; not clear
24	Polypoid solid adenocarcinoma (10.5 cm. diameter) projecting into lumen	+	Submucosa	II	3	12 mm.
25	14 cm. stomach; colloid carcinoma (10 by 6 cm.)	+	Submucosa	III	3	11 mm.
26	15 cm. stomach; adenocarcinoma (5.5 by 5 by 2 cm.)	+	Mucosa	III	3	7 mm.
27	12 cm. stomach; ulcerating fibrosarcoma (5 by 5 by 2 cm.)	—	Submucosa	..	3	5 mm.
28	13 cm. stomach; diffuse carcinoma	—	Serosa	IV	4	No edge
29	8 cm. stomach; carcinomatous ulcer (6 cm. diameter) with involvement of pylorus	..	Mucosa	III	3	10 mm.
30	12 cm. stomach; diffuse carcinoma	—	Mucosa	IV	3	Not clear; no edge
31	Diffuse carcinoma (4 cm. diameter) with small area of ulceration (1 cm. diameter; linitis plastica type)	+	Submucosa	IV	4	30 mm.

TABLE 1.—*Summary of Material—Continued*

Case	Description of the Pathologic Condition	Involvement of Lymph Nodes	Plane of Maximal Extension	Classification by Extension	Broders' Grading	Distance of Lateral Extension
32	13 cm. stomach; carcinoma (4 by 4 by 1.5 cm.) at pylorus; very few nodes attached	—	Mucosa	IV	4	8 mm.
33	12 cm. stomach; papillary adenocarcinoma (9 by 7 by 1.5 cm.)	—	Mucosa	II	2	No extension
34	12 cm. stomach; papillary carcinoma (7 by 6 by 2 cm.)	+	Submucosa	II	2	No extension
35	Ulcerated carcinoma (4 by 4 by 1.5 cm.); very few nodes attached	—	Submucosa	III	4	10 mm.
36	Stomach; carcinoma (5.5 by 4 by 1 cm.)	—	Submucosa	III	3	No extension
37	Portion of stomach; polypoid adenocarcinoma (6 by 5 by 3 cm.) projecting into lumen	—	Mucosa	II	2	No extension
38	15 cm. stomach; diffuse small cell carcinoma with very early colloid changes	—	Submucosa	IV	4	No edge
39	12 cm. stomach; adenocarcinoma (4 by 4 by 1 cm.)	..	Serosa	II	3	No extension
40	12 cm. stomach; shallow carcinomatous ulcer (5 cm. diameter); no nodes attached	..	Submucosa	IV	4	Not clear; at least 20 mm.
41	Carcinomatous polyp (9 by 6 by 6 cm.)	+	Mucosa	II	2	No extension; multicentric
42	Carcinomatous ulcer (6 cm. diameter; linitis plastica type)	—	Submucosa	IV	4	No edge
43	12 cm. stomach; carcinomatous ulcer (4 by 4 by 1.5 cm.)	+	Submucosa	IV	4	No extension
44	9 cm. stomach; carcinomatous ulcer (6 by 5 by 1 cm.)	+	Serosa	II	3	No extension
45	9 cm. stomach; adenocarcinoma (7 by 9 by 2 cm.)	+	Submucosa	II	2	No extension
46	13 cm. stomach; ulcerated and perforated adenocarcinoma (8 by 9 by 2 cm.)	+	Submucosa	II	2	No extension
47	14 cm. stomach; ulcerated carcinoma (4 by 4 by 1 cm.)	+	Serosa	IV	4	Not clear; at least 35 mm.
48	12 cm. stomach; carcinomatous ulcer	+	Serosa	IV	4	25 mm.
49	9 cm. stomach; adenocarcinoma (3 by 3 by 1 cm.) just above pylorus; in places producing colloid	+	Serosa	IV	4	No edge; 5 mm.
50	12 cm. stomach; ulcerated carcinoma (6 by 5 by 2 cm.) with involvement of serosa	—	Submucosa	II	2	No extension

quently is most likely to pass through hidden, lateral extensions in the apparently healthy gastric wall. Second, the lesser curvature is more abundantly supplied with lymphatic structures than any other part of the stomach, and, as it is known that carcinoma habitually extends by the lymphatic system, the farthest extensions of the growth would naturally be expected to be on the lesser curvature.

Occasionally it was found that the tumor did not reach the lesser curvature; in these cases the block was cut parallel to the lesser curvature and as near it as possible. Care was taken to include part of the tumor in the block, as well as all the apparently healthy tissue between the tumor and the resected edge of the stomach. In some cases the edge of the tumor was indistinct, and in these I used my judgment with regard to the edge. In other cases it was impossible to identify any edge of the tumor; these tumors were noted as having "no edge."

Cutting of Frozen and Paraffin Sections from Block.—The frozen and paraffin sections were stained in the usual manner with hematoxylin and eosin. Both groups of slides were subjected to microscopic examination.

Microscopic Examination of Slides.—The macroscopic edge of the tumor was first marked on the slide, that is, the "raised edge," indicated in figure 1. The carcinoma was then followed out to the point of maximal extension from the edge. This point was also marked on the slide, and the distance between the two points was measured in millimeters. At the same time, the plane of maximal extension in the gastric wall was noted.

Classification of Tumor According to Anatomic Manner of Extension from Edge of Growth.—The tumors were originally placed in three classes, I, II and III. Broders, in grading these tumors, did not find any which could be graded I; consequently, to avoid confusion, the original three classes were raised to II, III, and IV, so as to coincide with Broders'[11] grading. In class II, then, there was little if any lateral extension; in class III, moderate lateral extension, and in class IV, much lateral extension.

Study of Differentiation, Lymphocytosis and Fibrosis (MacCarty[12]).—These factors have been shown to bear a definite relation to the period of survival following removal of carcinoma. Lymphocytosis and fibrosis are part of nature's defensive mechanisms against the advance of carcinoma. Lymphocytosis was frequently noted, and in its presence the advance of the carcinoma appeared to be retarded. Fibrosis was not observed, except to a slight extent.

Grading According to Broders.—Broders himself graded each of these tumors after my classification was already recorded. It will be shown that classification and grading gave similar results.

RESULTS

With regard to the plane of extension, gastric carcinomas can be placed in three other groups according to whether they extend farthest in the mucosa, submucosa or serosa. Figure 1 indicates the manner in which carcinoma extends into the gastric wall.

The majority of carcinomas spread in the manner of the uppermost diagram in figure 1. It is seen that the tumor extends outward in the submucosa to a point well removed from the apparent limit of the disease. This extension in the submucosa takes place subjacent to healthy mucosa; there is nothing to indicate that the underlying tissues are affected. It might be supposed that the edge of the ulcer marked the limit of the disease; however, only microscopic examination can reveal the true state. The carcinoma extends first from the mucosa, through the muscularis mucosa, into the submucosa. Here its rapid extension is favored both by the rich supply of lymphatic channels and by the

11. Broders, A. C.: Squamous-Cell Epithelioma of the Lip. A Study of Five Hundred and Thirty-Seven Cases, J. A. M. A. **74**:656 (March 6) 1920.

12. MacCarty, W. C.: Factors Which Influence Longevity in Cancer. A Study of 293 Cases, Ann. Surg. **76**:9 (July) 1922. MacCarty, W. C., and Kehrer, J. K. W.: Possible Defensive Factors in Cancer of the Rectum. A Study of 102 Cases, J. Lab. & Clin. Med. **7**:602 (July) 1922. Sistrunk, W. E., and MacCarty, W. C.: Life Expectancy Following Radical Amputation for Carcinoma of the Breast. A Clinical and Pathologic Study of 218 Cases, Ann. Surg. **75**:61 (Jan.) 1922. MacCarty and Mahle.[5]

loose areolar tissue which offers little resistance to the advancing cells [13] (figs. 2 and 3).

The muscular coats of the stomach offer great resistance to the advancing carcinoma, and the cells of the tumor are usually found going through the muscular coats by way of the intermuscular lymphatic structures, to reach the serosa, where another rich network of lymphatic channels favors their rapid extension.

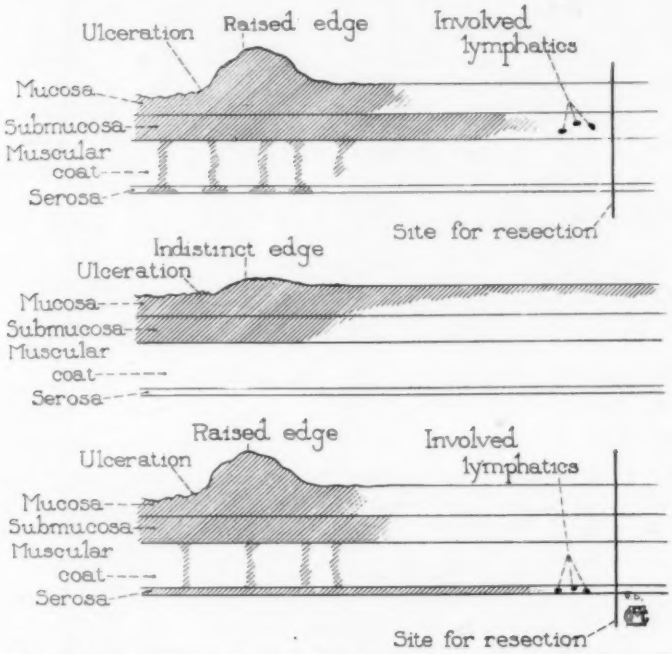

Fig. 1.—The manner of extension of carcinoma in the gastric wall.

The favorite plane for lateral extension in the gastric wall is the submucosa. Of fifty cases, maximal extension was in the submucosa in twenty-nine, in the mucosa in eleven, in the serosa in eight, in both the submucosa and serosa in one and in all coats in one. Extension in the mucous and serous coats remains to be considered.

It has been noted that the main extension was in the mucosa in eleven cases. This extension manifests itself in three ways. The first is the obvious and familiar polypoid carcinoma; these tumors have no deceptive underground ramifications. They have long been regarded as relatively harmless. W. W. Mayo [14] used to remark that the carcinoma

13. Jamieson, J. K., and Dobson, J. F.: The Lymphatic System of the Stomach, Lancet **1**:1061 (April 20) 1907.

14. Mayo, W. W., quoted by Broders.[11]

Fig. 2 (case 4).—Typical mode of extension in the submucosa; carcinoma 8 mm. from the edge of the ulcer.

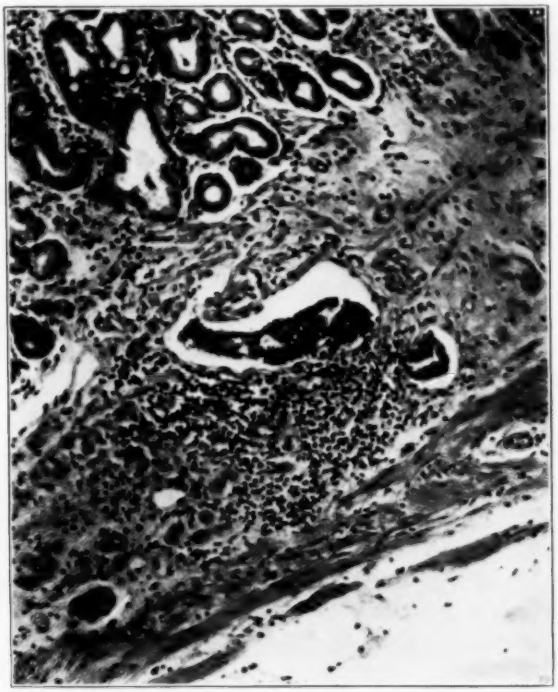

Fig. 3 (case 13).—Outlying malignant cell nest in the submucosa 11 mm. from the edge of the ulcer; × 125.

that grows toward one is not as dangerous as that which grows away from one.

The second type of carcinoma which has its main extension in the mucosa is diagrammatically represented in the middle section of figure 1. This type was present only twice (cases 21 and 30). Here the carcinoma was found spreading on the surface of the mucosa, over and between normal gastric glands. The impression I received was that this type of carcinoma spreads over the surface so rapidly that it does not have time to attack the deeper parts of the mucosa. In the two cases mentioned, the carcinoma extended down to the submucosa in the older part of the tumor. There was no visible edge (figs. 4, *A* and *B*). This is a very deceptive type from the surgeon's point of view, for the tumor has no visible edge, nor is there any thickening of the gastric wall which might help him to define the limits of the disease. Fortunately, this condition is comparatively rare.

In the third type in which extension is in the mucosa the extension may reach its maximal distance from the visible edge of the growth by involving the whole thickness of the mucosa without penetrating the submucosa. Case 32 illustrates this point; the submucosa had been penetrated at the older part of the tumor, but the extension, while involving the whole thickness of the mucosa, did not penetrate the muscularis mucosa (figs. 5, *A* and *B*).

Finally, the maximal plane of lateral extension may be in the serosa; this occurred, as has been noted, eight times in this series of fifty cases. When carcinoma involves the serosa, for some reason or other it fails to extend very far in the submucosa, but traverses the intermuscular lymphatic channels to reach the serosa, where its maximal extension takes place (fig. 6). The lowermost diagram in figure 1 illustrates this type of extension in the serosa, where rapid extension is favored by the abundance of lymphatic channels. It is interesting to note that in this series of fifty gastric carcinomas, in six cases lateral extension was more than 20 mm. from the edge of the growth, and in five of these the serosa was the plane of maximal lateral extension. In one of these five cases all coats were equally involved and in another the submucosa and serosa were involved to the same extent. In this series there was not a case of involvement of the serosa without metastasis to lymph nodes.

From the foregoing statements it will be obvious that in many cases the raised, palpable edge of a gastric carcinoma does not indicate the line of demarcation between diseased and healthy tissue; therefore, I was led to try to find some means of estimating the extent to which a given carcinoma will be likely to invade the surrounding gastric wall. It was found that an estimate could be made in two ways: A study of the differentiation of the tumor according to MacCarty will give a rough

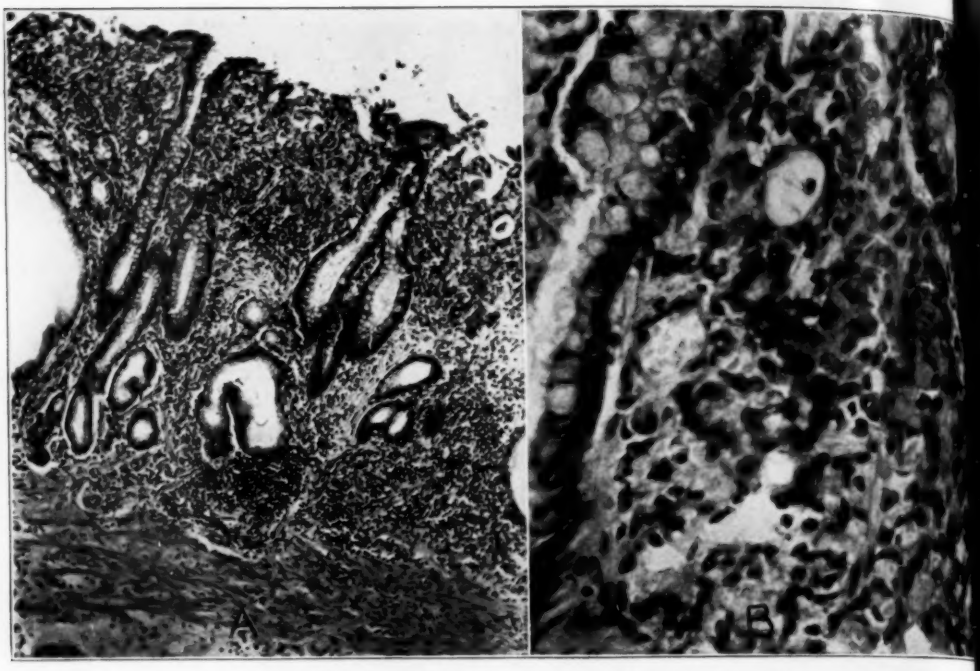

Fig. 4 (case 30).—*A*, diffuse spread of carcinoma over surface of stomach. *B*, higher magnification of part of *A*. The large "one-eyed" cell can be identified in both photomicrographs.

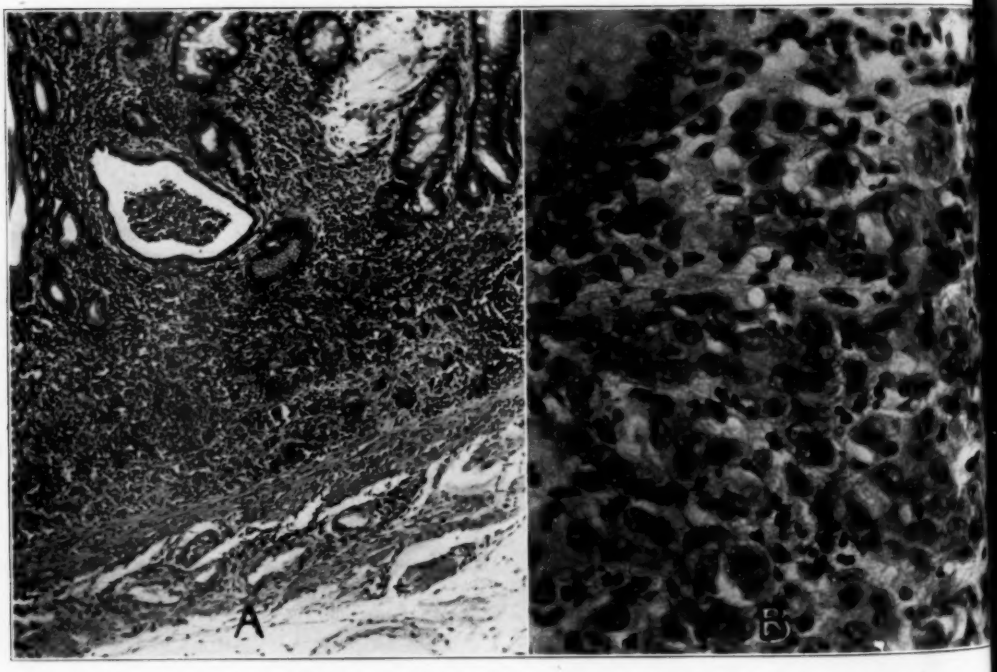

Fig. 5 (case 32).—*A*, another form of spread limited to the mucosa; cells 8 mm. from edge of ulcer. *B*, higher magnification of *A* showing malignant cells.

indication, as will the system of grading according to Broders. I shall correlate the grading of the tumors by Broders' method with the classification by the amount of lateral extension. It will be shown that the greater degree of lateral extension is to be expected among carcinomas of higher grade. The same principle is true of the differentiation of tumors according to MacCarty; the less the differentiation of the cells, the more likely is the tumor to have wide lateral extension. The grad-

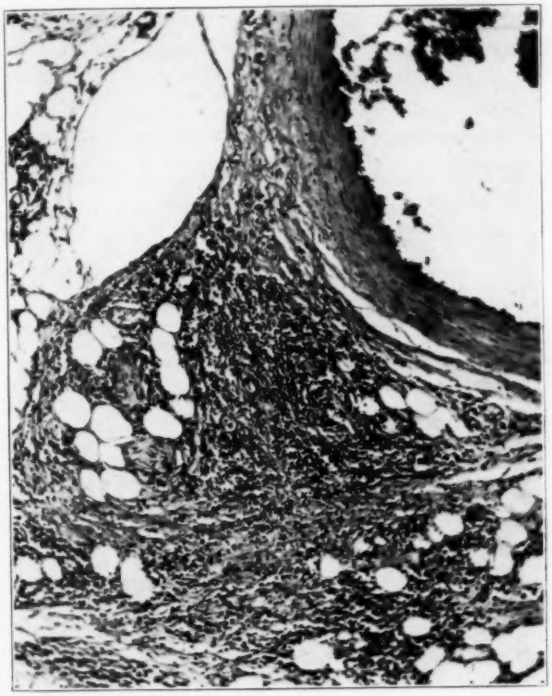

Fig. 6 (case 48).—Malignant cells in the serosa, 25 mm. from the edge of the ulcer.

ing, differentiation, and amount of lateral extension appeared in many cases to be parallel. For the guidance of those who wish to compare the two methods, differentiation and grading, it can be said that tumors of grade 2 are fairly well differentiated, those of grade 3, poorly differentiated, and those of grade 4, undifferentiated.

The fifty carcinomas were studied to determine the lateral extension in millimeters according to their grading by Broders' method. In eleven cases (cases 1, 6, 9, 19, 33, 34, 37, 41, 45, 46 and 50) in which the carcinomas were of grade 2, there was apparently no lateral extension. In table 2 it can be seen that carcinomas of grade 3 extend widely and that those of grade 4 extend most widely.

A little explanation is needed for those extensions and their measurements. Any carcinoma that extended less than 5 mm. was regarded as not having any lateral extension. In some cases the surgeon was unable to resect clear of the growth, and these cases are indicated by the words "not clear." In most cases the edge of the tumor was distinct, and the limit of malignant extension into healthy tissue could be distinguished. However, these measurements are not absolutely accurate, for it is impossible to measure a series of carcinomas to a millimeter. Nevertheless, it should be remembered that the personal error is common to all the specimens, and the figures are sufficiently accurate to bring out some interesting points.

TABLE 2.—*Amount of Lateral Extension of Gastric Carcinomas*

20 Carcinomas, Graded 3		19 Carcinomas, Graded 4	
Case	Lateral Extension in Millimeters	Case	Lateral Extension in Millimeters
2	10	3	30 (not clear)
4	8	7	No extension
5	No edge	8	5 (not clear)
10	No extension	14	5 (not clear)
11	10	15	10
12	6	16	5
13	11	17	8
18	5	20	40 (not clear)
21	No edge (not clear)	28	No edge
22	10	31	30
23	22 (not clear)	32	8
24	12	35	10
25	11	38	No edge
26	7	40	20 (not clear)
27	5	42	No edge
29	10	43	No extension
30	No edge (not clear)	47	35 (not clear)
36	No extension	48	25
39	No extension	49	No edge
44	No extension		

Among the carcinomas graded 3 (table 2), in three instances the surgeon did not resect clear of the growth; in two of these cases the tumor had no visible edge. It is interesting to note that both these tumors were of the unusual type which extends solely over the surface of the mucous membrane. At the oldest part of the neoplasm there was some extension downward into the submucous and muscular coats, but all of the lateral extension was over the surface of mucous membrane of the stomach; the carcinomatous material looked as if applied like a coat of paint. These tumors were both classified by MacCarty as undifferentiated tumors and highly malignant. In such circumstances the surgeon has no means of estimating at what point his resection should be carried out, and extends it as high on the lesser curvature as possible. In the third case in which the surgeon failed to resect clear of the growth it had extended 22 mm. from the edge of the ulcer. This was case 23, and it will be noted that the maximal extension was in the

serosa. On consulting the history of this case it was found that the patient had had symptoms for two years, or thirteen months longer than the average history given in cases of gastric carcinoma in the clinic (McVicar[15]). It is conceivable that if a carcinoma is left long enough, especially if there is involvement of the serosa, there is practically no limit to the possible distance of the extension. It may be stated that as a rule carcinomas graded 3 may extend a distance of 15 mm. from the visible edge of the ulcer. The average lateral extension in the sixteen carcinomas graded 3 measured 6.56 mm.

On six occasions the line of resection was through the growth in spite of the fact that on four occasions the gastrectomy was done at least 20 mm. from its edge. Cases 7 and 43 (table 2), in which there was no lateral extension, require a little explanation. The tumors in both of these cases were very active, and belonged to the class of "small cell" carcinoma; in fact, they resembled lymphosarcoma, and there was discussion before it was decided to call the tumor in case 7 small cell carcinoma and not lymphosarcoma. Another point of similarity in these two tumors was the very active lymphocytic barrier thrown out by the tissues against the advancing malignant cells. I would suggest that these were two very active and rapidly advancing tumors which did not have sufficient time to send out the usual offshoots. The growth was so rapid that the edge of the tumor kept moving centrifugally. It will be observed that on one occasion the resection was carried out about 40 mm. away from the edge of the tumor, yet the surgeon was unable to remove all of it. The average extension of nine carcinomas graded 4 was 10.66 mm.

Only sixteen of twenty carcinomas graded 3 and only nine of nineteen graded 4 could be measured from the edge of the ulcer to the limit of lateral extension; that is, in some there was not a definite edge from which to measure, and in others the resection was done through tumor cells. However, if tumors of both grades in which there was "no edge" are excluded, but if those which bear the notation "not clear" are included, measuring these up to the line of resection, more reliable material is obtained from which to make deductions. By this plan, the average lateral extension in seventeen carcinomas graded 3 was 7.47 mm. and in fifteen carcinomas graded 4 it was 15.4 mm. Broadly speaking, the carcinomas of various grades extend as would be expected; extension of those of grade 3 is about halfway between the extensions of those of grades 2 and 4. Apparently, this classification is also borne out by the difficulties of the surgeon. Of eleven cases of carcinoma graded 2, there was no lateral extension in any, and all were resected clear of

15. McVicar, C. S., and Daly, Joseph: The Diagnosis of Operable Carcinoma of the Stomach, Ann. Int. Med. **1**:145 (Sept.) 1927.

the growth. Of twenty cases in which the carcinoma was graded 3 there was no lateral extension in four cases; lateral extension was between 5 and 22 mm. in twelve cases, and resection was not clear of the

TABLE 3.—*Distance and Plane of Extension in Cases in Which There Was No Involvement of Lymph Nodes*

Case	Grade	Distance in Millimeters	Plane of Maximal Extension
1	2	10	Submucosa
2	4	10	Submucosa
7	4	No extension	Submucosa
12	3	6	Submucosa
16	4	5	Submucosa
22	3	10	Submucosa
27	3	5	Submucosa
30	3	No edge (not clear)	Mucosa
32	4	8	Mucosa
33	2	No extension	Mucosa
35	4	No extension	Submucosa
36	3	No extension	Submucosa
37	2	No extension	Mucosa
38	4	No edge	Submucosa
42	4	No edge	Submucosa
50	2	No extension	Submucosa

TABLE 4.—*Distance and Plane of Extension in Cases in Which There Was Involvement of Lymph Nodes* *

Case	Grade	Distance in Millimeters	Plane of Maximal Extension
3	4	30	Submucosa, serosa
4	3	8	Submucosa
5	3	No edge	Submucosa
6	3	No extension	Submucosa
8	4	Not clear	Submucosa
9	2	No extension	Submucosa
10	3	No extension	Submucosa
11	2	No extension	Mucosa
13	3	11	Submucosa
14	4	Not clear	Mucosa
15	4	10	Mucosa
17	4	8	Submucosa
18	3	5	Serosa
19	2	No extension	Submucosa
20	4	Not clear	All coats
23	3	Not clear	Serosa
24	3	12	Submucosa
25	3	11	Submucosa
26	3	7	Mucosa
31	4	30	Submucosa
34	2	No extension	Submucosa
41	2	No extension	Mucosa
43	4	No extension	Submucosa
44	3	No extension	Serosa
45	2	No extension	Submucosa
46	2	No extension	Submucosa
47	4	Not clear	Serosa
48	4	25	Serosa
49	4	No edge	Serosa

* Five cases with involvement of nodes not included.

growth in three cases. Of nineteen cases of carcinoma graded 4, there was no lateral extension in two cases; lateral extension was between 5 and 40 mm. (in five, more than 22 mm.) in thirteen cases, and resection was not clear of the growth in six cases.

In tables 3 and 4 is given the amount of lateral extension of carcinomas of the stomach without and with nodal involvement, respectively.

It will be seen that the carcinomas of the stomach with nodal involvement extended more widely than those without involvement, and that most of the resections which did not include the whole of the tumor were performed in those cases in which there was nodal involvement.

SUMMARY AND CONCLUSIONS

In gastric carcinomas the raised, rampart edge of the ulcer may not mark the limit of invasion of the gastric wall. The amount of extension from the edge of a gastric carcinoma varies according to the degree of differentiation (MacCarty) and the grading (Broders). In the most diffuse carcinomas of the stomach, the growth has no visible edge, and a proper point for resection cannot be indicated; in all other types of gastric carcinoma a distance of at least 4 cm. of healthy gastric wall should be allowed from the edge of the ulcer along the lesser curvature toward the cardia, in order that the resection may include the whole of the primary focus. This small series tends to indicate that whenever the serosa is involved, nodal metastasis will be present.

CHRONIC PANCREATITIS ASSOCIATED WITH PEPTIC ULCER

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The conservative treatment of peptic ulcer is generally admitted by internists and surgeons to be the proper procedure to follow as long as symptomatic relief can be obtained. The difficulty comes in determining when the patient will not respond further to medical care and must be operated on. It is my experience [1] that one need not fear that a gastric ulcer will become malignant; at least, this should not be used as an argument for referring patients for operation, since the mortality due to gastric resection in the hands of experienced surgeons exceeds the incidence of malignant transformation. In the clinic with which I have been associated, patients with gastric ulcer have received conservative treatment for the past five years without malignant degeneration.

There is one true indication for operation, and that is uncontrollable pain, which is rarely due to an uncomplicated ulcer but results when an adjacent viscus becomes adherent to the ulcerated area. In the majority of instances the organ involved is the pancreas, which becomes chronically infected; at least, the enlargement and induration of the pancreas must be clinically attributed to chronic infection. There is a great deal of discussion as to the etiology of chronic interstitial pancreatitis, but in this presentation I shall not enter into the theories of the disease, which have been discussed in a previous presentation.[2] I shall consider only the clinical significance of pancreatic lesions in relation to peptic ulcer.

In the gastro-enterologic clinic of the Fourth Medical and Surgical Divisions of Bellevue Hospital, which ended its fifth year in December, 1932, my associates and I had occasion to observe 583 patients suffering from peptic ulcer. Of this group there were 440 who were not operated on and 143 who had been operated on before entering the clinic. Of the patients operated on, 71 were operated on for chronic ulcer and 72 for

1. Hinton, J. W.: The Clinical Consideration of Gastric Ulcer and Carcinoma, Arch. Surg. **27**:395 (Aug.) 1933.

2. Hinton, J. W.: Chronic Interlobular Pancreatitis, Ann. Surg. **96**:441 (Sept.) 1932.

acute perforated ulcer. It was the purpose of the clinic to determine the best method or the best combination of methods to be used in treating these patients conservatively; therefore we referred patients for operation only as a last resort. The one indication which was accepted as a true indication for surgical intervention was pain which no method of medical treatment would relieve. During this period of five years we referred only 33 patients from the clinic for operation. In some of these cases the associated pancreatitis was so striking that the cases seem worthy of reporting.

REPORT OF CASES

CASE 1.—A man, aged 52, was admitted to the Fourth Surgical Division, Bellevue Hospital, on Jan. 26, 1928. He had been operated on in another hospital on Dec. 15, 1927.

He was jaundiced, and complained of abdominal pain. He was receiving ⅙ grain (0.01 Gm.) of morphine three times a day. A résumé of the operative findings from the other institution was: carcinoma of the head of the pancreas with metastasis to the spine. In view of this diagnosis, it was thought advisable to make a roentgenologic examination of the intestinal tract, in order to demonstrate the pancreatic tumor. Roentgenologic study revealed, however, that the patient had a duodenal ulcer. A Sippy diet was instituted. Within one week the patient had so improved that he was no longer given morphine. He was discharged from the hospital on Feb. 12, 1928, and was followed in the gastro-enterologic clinic until April 23. On this date he was readmitted to the hospital because of severe pain which he had had for two weeks; previous to this, however, he had been symptomatically well for two months. Dr. John H. Morris operated on the patient on April 26. An ulcer was found in the duodenum with an induration of the head of the pancreas the size of a large lemon. A gastro-enterostomy was performed; the gallbladder and appendix were found to be normal and were not removed. After the operation, the patient was followed regularly in the clinic; he had no jaundice but had frequent complaints referable to the bladder. The results of urologic examinations were of no significance. The patient was last seen on Jan. 26, 1933.

CASE 2.—A man, aged 52, was admitted to the gastro-enterologic clinic of the Fourth Medical and Surgical Divisions at Bellevue Hospital on Jan. 12, 1929, with a roentgenologic diagnosis of pyloric ulcer. The patient was given a Sippy diet and was symptomatically well until September 28. Roentgenograms on June 14 and on October 3 revealed no abnormalities. When the symptoms recurred the pain could not be relieved by conservative treatment, although a series of roentgenograms of the gastro-intestinal tract showed nothing abnormal. The patient was advised to enter the hospital. I operated on him on November 9. When the abdomen was opened, the gallbladder was found to be normal; the duodenum was mobile and easily inspected; there was no evidence of ulcer on the anterior surface, but a slightly indurated area was felt posteriorly, and the head of the pancreas was the size of a lemon. A posterior gastro-enterostomy and an appendectomy were performed, from which the patient made an uneventful recovery. He was followed regularly in the clinic; he remained symptomatically well and roentgenologically normal. He was last seen on Jan. 19, 1933.

CASE 3.—A man, aged 59, was admitted to the hospital on Aug. 21, 1930, complaining of epigastric pain after meals, with periodicity for twenty years; during the two years prior to admission he had had persistent pain which was more severe at night. Roentgenologic examination on August 15 revealed a duodenal ulcer without obstruction. A Sippy diet was tried for two weeks, without affording the patient relief. Operation on September 5 revealed the gallbladder to be olive green and not thickened, but there was a duodenal ulcer with the duodenum fixed to the pancreas, and the head of the latter organ felt the size of a lemon. A posterior gastro-enterostomy without clamps and a routine appendectomy were performed. Convalescence was uneventful; the patient improved, but still experienced some discomfort. He was last seen on Jan. 5, 1933.

CASE 4.—A man, aged 32, was admitted to the clinic on Dec. 1, 1928, complaining of abdominal pain after meals. He had had these attacks for seven years and for the last year the pain had been severe; food gave little relief. Roentgenologic study on Nov. 25, 1928, had revealed a duodenal ulcer without obstruction. The patient was given an ambulatory Sippy diet, wtihout relief, and then was given streptococcus vaccine. After four and a half months of conservative treatment his condition had not improved; he was having pain at night constantly. Operation on April 25, 1929, disclosed a duodenal ulcer, with the pancreas enlarged and the duodenum adherent to the gland. A posterior gastroenterostomy without clamps and a routine appendectomy were performed. The gallbladder was thickened and chronically diseased, but it was not removed, owing to the fact that the patient had shown poor anesthesia. An uneventful convalescence followed. The patient was observed regularly after leaving the hospital; he remained symptomatically improved, but was not entirely well. He was last seen on Dec. 29, 1932.

CASE 5.—A woman, aged 36, was admitted to the clinic on March 17, 1928, complaining of periodic pain after meals. She had entered Bellevue Hospital on June 15, 1925, because of pain in the right upper quadrant of the abdomen which was cramplike and which radiated to the right shoulder. At that time she also complained of pain after meals, which, however, was relieved by food. A diagnosis of cholecystitis and cholelithiasis was made, and the patient was operated on on June 20. A chronic cholecystitis was found but no stones. Also a duodenal ulcer was found which was pronounced healed. A cholecystectomy was performed, but the stomach was not operated on. The patient was readmitted on Dec. 21, 1925, complaining of pain in the upper part of the abdomen which had been present for three months. The pain was similar to that for which she had been operated on before. Roentgenologic examination revealed a duodenal ulcer, and the patient was given a Sippy diet. She remained in the hospital until Jan. 12, 1926, and was discharged symptom-free, but was readmitted on May 26 because of pain. Roentgenologic study revealed a duodenal ulcer. The patient was operated on on June 3, but the operating surgeon, who also performed the first operation, did not find an ulcer; so the abdomen was closed. The patient returned to the follow-up clinic at irregular intervals for the next year and a half but was constantly complaining of pain.

On entering our clinic, March 17, 1928, the patient stated that she had not been relieved by either operation, and that she was much worse than before. Her chief complaint was pain after meals, which was usually relieved by food; the pain was becoming so severe that it kept her awake at night. Roentgenologic study revealed a duodenal ulcer. The patient was given medical treatment, but she was uncooperative, returning only at irregular intervals. A year later she

was advised to permit herself to be operated on, as her condition was growing worse, but she refused. She returned to the clinic at irregular intervals until Sept. 5, 1930, when the pain became so severe that she entered the hospital of her own accord. She was operated on on September 12. The duodenum was found to be adherent to the pancreas, and the head of the latter was enlarged to the size of a large lemon. A posterior gastro-enterostomy was done. The patient was greatly improved. When last seen on Feb. 2, 1933, she complained of gas after meals, but had no pain.

Case 6.—A man, aged 30, was admitted to the clinic on July 7, 1929, complaining of pain in the upper part of the abdomen. The history was unimportant. The patient had had epigastric discomfort for ten years. Eating gave relief from the symptoms, which were probably never very severe, as the patient first sought medical treatment two weeks before admission. At that time a roentgenogram revealed a duodenal ulcer. The patient was given an ambulatory Sippy diet and did well for four months; then his symptoms returned, and he was given vaccines, without improvement. The patient gained 20 pounds (9 Kg.) while under treatment; he was heavier than ever before, his weight being 180 pounds (81.6 Kg.). The medical treatment was continued until May 20, 1930, when he was advised to enter the hospital for operation, although he had maintained his weight. Operation on May 24 revealed a duodenal ulcer and an adhesion of the duodenum to the pancreas, with the head of this organ enlarged and firm. A posterior gastro-enterostomy was performed, and the patient was symptom-free thereafter. He was last seen on Sept. 28, 1932.

Case 7.—A man, aged 57, was admitted to the hospital on Oct. 9, 1930, complaining of severe abdominal pain; he said that he had been treated for an ulcer. For twenty years the patient had had pain after meals, and for fifteen years he had known that he had an ulcer, for he had been treated for it by different physicians. Eight weeks before coming under our observation, he was under the care of a prominent gastro-enterologist and was treated with a duodenal tube for four weeks. The pain was so severe that he was unable to sleep, and owing to the severe pain he was referred to the hospital with a diagnosis of complicating cholecystitis and cholelithiasis, though the dye test was negative. After admission the patient required codeine for the pain; he refused to have further roentgenograms of the gastro-intestinal tract made; an exploratory laparotomy was therefore performed on October 15, which revealed a normal gallbladder, a duodenal ulcer and an enlargement of the pancreas to the size of an orange. A posterior gastro-enterostomy and a routine appendectomy were performed; following the operation the patient was fairly free from symptoms. However, he had two exacerbations of symptoms. He was last seen on Dec. 29, 1932.

Case 8.—A man, aged 30, was admitted to the clinic on April 28, 1931, stating that he had been treated in the medical wards for an ulcer. A résumé of the hospital records revealed that he had entered the wards on April 3, and that he had been discharged on April 25. He gave a history of epigastric distress of six years' duration, which was getting more severe. Roentgenologic examination revealed a duodenal ulcer without retention at the end of six hours. The patient was treated by a Sippy diet while in the hospital, and was discharged improved. He did not continue to receive treatment at the clinic, but on October 4, having severe pain, he entered the emergency ward; there he was advised to go to the hospital as a ruptured ulcer was suspected. On examination, the diagnosis of duodenal ulcer and chronic pancreatitis was made, and an operation was advised. The operative findings on October 9 were chronic cholecystitis, duodenal ulcer and

chronic pancreatitis, as the head of the gland was the size of a lemon. A cholecystectomy, appendectomy and posterior gastro-enterostomy were performed. The patient improved after the operation. He was last seen Nov. 17, 1932.

Case 9.—A man, aged 38, was admitted to the hospital on July 17, 1931, complaining of abdominal pain after meals. The history was not important except for the illness in question. The patient had had pain in the upper abdominal region for ten years and during the two years prior to admission it had been much more severe. He was treated in the medical wards from June 10 to June 29 and given a Sippy diet. Roentgenologic study revealed a duodenal ulcer without retention at the end of six hours. A vitamin diet with yeast was instituted without relief; the diet was then changed to an ambulatory Sippy diet with Saunders' streptococcus vaccine intravenously, without relief. On August 29, owing to the severe pain and a diagnosis of duodenal ulcer and pancreatitis, the patient was advised to enter the hospital. Operation on September 3 revealed a duodenal ulcer and an enlarged pancreas, with the duodenum adherent to it. The gallbladder was normal. A posterior gastro-enterostomy and a routine appendectomy were performed, but the patient continued to have pain. After persistent medical care, without relief of pain, a subtotal resection was performed on Oct. 10, 1932. The patient died of pneumonia six days afterward.

Case 10.—A man, aged 25, was admitted to the hospital on Dec. 30, 1929, complaining of abdominal pain after meals. The history except for the illness revealed nothing of consequence. The patient stated that he was seized with severe pain on July 5, and that he was operated on for a ruptured ulcer in the Jersey City Hospital. A report from that hospital was to the effect that the operation had revealed a ruptured duodenal ulcer, and that a simple closure had been performed. The patient said that he had had abdominal discomfort after meals for two years before the perforation occurred, and that following the operation he was well for two months, but that for the past four months he had had abdominal pain after meals, which was getting worse. Roentgenologic study on Jan. 3, 1930, revealed a duodenal ulcer without retention at the end of six hours. He was treated in the wards for one week and then referred to the clinic, which he entered on January 11. An ambulatory Sippy diet, Saunders' vaccine, administered intramuscularly, and nonspecific protein therapy with a milk preparation failed to give permanent relief, and the patient was admitted to the hospital on October 20 for operation, with the diagnosis of duodenal ulcer and chronic pancreatitis. Operation on October 25 revealed a duodenal ulcer and enlargement of the pancreas to the size of a large lemon, with the duodenum adherent to it. The gallbladder was normal. A posterior gastro-enterostomy and appendectomy were performed. The patient remained clinically well. He was last seen on Jan. 12, 1933.

Case 11.—A man, aged 39, was admitted to the clinic on July 10, 1930, complaining of abdominal pain after meals and severe pain at night. The history except for the illness was not significant. Since 1914 the patient had had abdominal pain after meals, and in 1916 the condition was diagnosed as ulcer. In 1917 the patient was operated on in Dublin, Ireland. The ulcer was found, but it was pronounced healed; the appendix was removed. The patient obtained no relief from the operation; his condition became gradually worse, and at night he was kept awake from one to two hours with pain. Roentgenologic study revealed a duodenal ulcer with retention at the end of six hours. The patient was treated with an ambulatory Sippy diet and was given Saunders' vaccine intramuscularly, with only slight relief. He refused to enter the hospital for rest in bed, as he had

been treated in two other hospitals during the past year by a Sippy diet with only slight improvement. After five months of treatment, operation was advised; the diagnosis was duodenal ulcer and chronic pancreatitis. On Dec. 12, 1930, the operation was performed; it disclosed chronic cholecystitis, a duodenal ulcer and an enlarged, firm pancreas adherent to the duodenum. A posterior gastro-enterostomy and cholecystectomy were performed. Following the operation, the patient was well for one year, but at that time had a moderate hemorrhage. He has not been seen since.

Case 12.—A man, aged 25, was admitted to the hospital on Sept. 4, 1931, complaining of severe abdominal pain that had lasted for two hours. The history revealed that on Dec. 29, 1929, he was operated on for perforated ulcer without suturation of the ulcer. Dr. Fischel, his family physician, stated that when the abdomen was opened, gas and free fluid escaped, but that the perforation was not found and cigaret drains were inserted. The patient made an uneventful recovery and was symptom-free until Sept. 4, 1931. Two hours before admission to the hospital he was seized with sudden abdominal pain, and Dr. Fischel again diagnosed the condition as perforated ulcer. The operation was performed by Dr. Briedenbach. On opening the abdomen, he found gas and free fluid, but he could not find the perforation, as the duodenum was adherent to the pancreas and the latter organ was enlarged. Drains were inserted, and an uneventful convalescence followed. The patient entered the clinic on September 24, and was followed regularly until October 23, when he had another attack of severe abdominal pain which necessitated admission to the hospital. During the observation in the clinic he was purposely not studied roentgenologically, as we feared that a perforation might result from the manipulation, but at about 4 a. m. on October 23, he was seized with sudden pain, and a boardlike rigidity set in. The operation was again performed by Dr. Briedenbach. When the peritoneum was opened, no gas or free fluid was encountered. The duodenum was adherent to the pancreas, and the latter was hard and twice its normal size. The capsule was perforated, and drains were inserted. Convalescence was uneventful. The patient was not followed after his departure from the hospital, as he left the city.

Case 13.—A woman, aged 47, was admitted on Feb. 14, 1930, complaining of severe colicky pain in the upper part of the abdomen of three weeks' duration. She had a hysterectomy in 1921 and an operation for disease of the gallbladder in 1923, but did not know whether or not the gallbladder had been removed. Since the operation for disease of the gallbladder she had had other attacks of rather severe pain in the upper abdominal regions, but none so severe as the cramplike pains which she had had in the last three weeks. Roentgenologic examination on Feb. 24, 1930, by the dye method did not reveal the gallbladder, and the series of roentgenograms of the gastro-intestinal tract revealed that the duodenal bulb was diminished, but showed no definite ulcer, although there was a retention of two thirds of the meal at the end of six hours. The preoperative diagnosis was cholecystitis and cholelithiasis. The patient was operated on on February 26 by Dr. Morris. An induration was found in the descending portion of the duodenum which was interpreted as an ulcer perforating into the pancreas. A posterior gastro-enterostomy was performed. Three days postoperatively pain and tenderness developed in the right lower quadrant which it was suspected were due to leakage from the ulcer. The area was opened, and the duodenal contents were obtained. The patient had a stormy convalescence, with three intra-abdominal abscesses, which were drained. She was discharged on May 5, and entered the clinic on May 24. The patient was symptom-free until November, when an abscess developed in the previous scar; she entered the hospital on November 7 and

remained until Jan. 5, 1931. After her discharge, she was symptom-free until October 1, when another abscess developed in the laparotomy scar. She entered the hospital on Octboer 23, and two abscesses were incised and drained; during the year of 1932 she entered the hospital twice with small abscesses in the previous scars and continued to have pain referable to the upper regions of the abdomen. She was last seen on Oct. 7, 1932, at which time she was having some epigastric discomfort.

The history is the most important aid to a diagnosis of chronic pancreatitis in the advanced stages. The patient usually says that his pain is more severe than at the onset of his complaints, and that the dull discomfort that he had when the ulcer was first diagnosed has disappeared. Food gives little relief, and he is awake several hours at night from pain, and frequently requires sedatives before he can sleep. The pain radiates directly through to the lumbar region and is usually felt on both the right and left sides of the spine. Physical examination reveals epigastric tenderness and a tenderness over the lumbar region which is equally marked on the right and left sides of the spine; the results of physical examination are otherwise negative. The routine laboratory work helps little in the prognosis of the course of ulcers. We used the amylase test of the blood serum according to Elman's method,[3] and the lipase test of the serum according to Cherry and Crandall's [4] method, in the hope of detecting cases of early chronic pancreatitis before the ulcer symptomatology had changed; it was hoped that with the infection and fibrosis of the pancreas the amylase and lipase would be constantly reduced in patients suffering from an associated pancreatitis, but our results were extremely variable and of no clinical significance; after using the tests on forty patients, we discontinued using them. While carrying out experiments on dogs in which we ligated the pancreatic ducts to produce thyroid changes, we studied the amylase and lipase of the blood of fifteen of these animals at weekly intervals until they died. The average life was four weeks, but some died within two weeks, while others lived eight weeks. Even in those animals in which a complete fibrosis of the pancreas developed, the results of the tests were most variable and could not be of clinical significance.

The selection of the time to operate in a case of peptic ulcer is of extreme importance. It is generally admitted that the results of operating early are unsatisfactory, regardless of the type of operation per-

3. Elman, Robert; Arneson, Norman, and Graham, E. A.: Value of Blood Amylase Estimations in the Diagnosis of Pancreatic Disease, Arch. Surg. **19**:943 (Dec. pt. 1) 1929.

4. Cherry, I. S., and Crandall, L. A.: The Specificity of Pancreatic Lipase: Its Appearance in the Blood after Pancreatic Injury, Am. J. Physiol. **100**:266 (April) 1932.

formed, while if the patient has suffered from the ulcer for a number of years, the results are more satisfactory following any operative procedure. The claim that the good results in cases of long standing come from some protective enzyme that develops in the blood and prevents marginal ulcers is mere speculation. I know, however, that operations thirty years ago gave satisfactory results. During the past ten years, in which patients have been referred for operation much sooner after the onset of symptoms, the surgical results have been generally unsatisfactory.

From clinical observations, it would seem that when a patient reveals the development of an associated pancreatitis, he ceases to present a medical problem; he should be operated on. To make the diagnosis of associated pancreatitis one must rely on the change in the pain symptomatology and on the clinical finding of tenderness over the regions of the kidneys with epigastric tenderness. After the infection of the pancreas has developed, delay in the operative treatment offers a more unfavorable prognosis.

I am aware of the emphasis that has been placed on cholecystitis as an etiologic and complicating factor in ulcers, but the more clinical and operative experience that I have with ulcers, the more I am impressed that there is only a slight relationship, either etiologic or symptomatic, between diseases of the biliary tract and peptic ulcers. The finding of an enlarged, firm pancreas, with the duodenum or the pyloric end of the stomach adherent to the gland, is of much more clinical significance and is a true indication for operative intervention. The indications that have been given for operating on ulcers, namely, a penetrating ulcer, a gastric ulcer, a pyloric obstruction, a gross hemorrhage and previous medical treatment, unless advanced by a competent internist, are not true indications for recommending surgery; the one indication is persistent pain that cannot be relieved by any method of medical care. The pain is usually due to an associated pancreatitis and is of a different character from that encountered in the early course of the disease. In 233 autopsies, Hurst and Stewart [5] found the pancreas forming the floor of the ulcer in 24.5 per cent of the cases, and the liver in 4.2 per cent; they also found in 183 partial gastrectomies that the pancreas formed the floor in 19.5 per cent and the liver in 1.5 per cent of the cases. With the ulcer and the pancreas in direct contact in such a high percentage of the cases, one would expect, clinically, to have a chronic infection of the pancreas which would alter the ulcer symptomatology, and that is what my associates and I have encountered.

5. Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcers, New York, Oxford University Press, 1929, pp. 106 and 189.

From the study of our cases it is seen that chronic pancreatitis is a real indication for operating on a patient with an ulcer, as it is a condition that cannot be cured by medical care. The difficulty is in diagnosing the condition in its early stage; one has been forced to rely chiefly on the history and physical findings, as the routine laboratory studies are of little aid. In a previous paper [6] I reported the laboratory observations in 141 cases, namely, the complete blood counts, the results of gastric analyses, the results of chemical examination of the blood, including determinations of the urea, nonprotein nitrogen, sugar, creatinine, chlorides, calcium and phosphorus, and the results of Wassermann tests and of urinalyses; in none of these cases was the laboratory work of any aid in prognosticating the course of either gastric or duodenal ulcer.

COMMENT

It is obvious to every one who has had experience in treating patients with ulcers that there are spontaneous remissions with freedom from pain for weeks, months and years; this makes it extremely difficult to evaluate the results from either medical or surgical treatment unless the patients are seen at frequent intervals and observed over an indefinite period.

When chronic pancreatitis is associated with ulcer, the sooner the diagnosis is made and the patient operated on, the better the chances for a good prognosis. So far there have been no accurate laboratory methods of making such a diagnosis, and one has been forced to rely on clinical findings in arriving at such a conclusion. Determinations of the amylase of the duodenal contents are now being made and may aid in detecting early chronic pancreatitis; if so, one will be in a position to select with much more accuracy the patients that need to be operated on. This may remove from the internist's care those patients in whom he cannot hope for a good result from medical treatment and turn over to the surgeon those for whom there will be a good prognosis following operation. It will eliminate operations on patients who may respond permanently to conservative treatment, and diminish the incidence of that serious complication, gastrojejunal ulcer, which follows too frequently gastro-enterostomy and occasionally subtotal gastrectomy.

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6. Hinton, J. W.: The Significance of Laboratory Studies in Gastric and Duodenal Ulcers, Am. J. Surg. **17**:25 (July) 1932.

DIGESTION OF BONE BY LARVAE OF PHORMIA REGINA

ITS RELATIONSHIP TO BACTERIA

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The use of living maggots as a therapeutic measure in osteomyelitis was introduced [1] by Baer in 1929. He found that this treatment brought about early complete healing of infections of the bone that had been resistant to other forms of accepted therapy. The cause of this rapid healing was debated by Baer, but remained an unsolved problem in his mind. He felt that the end-results were possibly due to the ingestion of dead tissue by the maggots or to the liberation of an enzyme. He mentioned the possibility of extracting some active substance or enzyme the use of which might replace the application of living maggots to wounds. Unfortunately, he was unable to investigate these problems, and a continuation of his work would seem to be well worthy of consideration. Since this subject entails numerous problems requiring various steps of investigation, it was felt that a study on larval digestion would prove a necessary and interesting prelude.

Fabre (1894) in his study of the green bottle fly observed rapid liquefaction of coagulated albumin in the presence of maggots. This he attributed to an active pepsin secreted by the larvae. Guyénot (1906-1907) reinvestigated this problem and made various extracts of maggots and of their salivary glands, but failed to secure liquefaction or digestion of proteins, carbohydrates or fats. He was able, however, to isolate Micrococcus flavus-liquefaciens, which he showed was capable of liquefying protein, and he attributed the digestive changes in the larvae to the action of this organism. Bogdanow (1906-1908) confirmed the findings of Guyénot. Wollman (1911) repeated the experiments of Bogdanow, and found that he was able to raise larvae aseptically by tyndallizing mediums instead of autoclaving them; he felt that coagulation made the mediums indigestible, and that bacteria were not the cause of digestion. Baer (1931) was able to raise maggots aseptically by feeding them a medium of beef, liver and yeast. The problem of aseptic growth has been dealt with and confirmed by other workers. Of further interest is the demonstration by Weinland (1906) of the digestion of fibrin in the excreta of the larvae of Calliphora. Hobson

1. For the history of the therapeutic application of maggots, antedating Baer's work, see Goldstein (1931) and Baer (1931).

(1931) showed, among other findings, the presence of a proteolytic enzyme in the excreta and intestines of the larvae of Lucilia sericata. The presence of enzymes capable of independent digestion has therefore been demonstrated in two species of larvae. Hobson has shown that the proteolytic enzymes present in Lucilia sericata can digest gelatin, elastin and white fibrous tissue collagen, but in view of the fact that no study was made on the digestion of bone, I determined to investigate the question of digestion of bone by larvae.

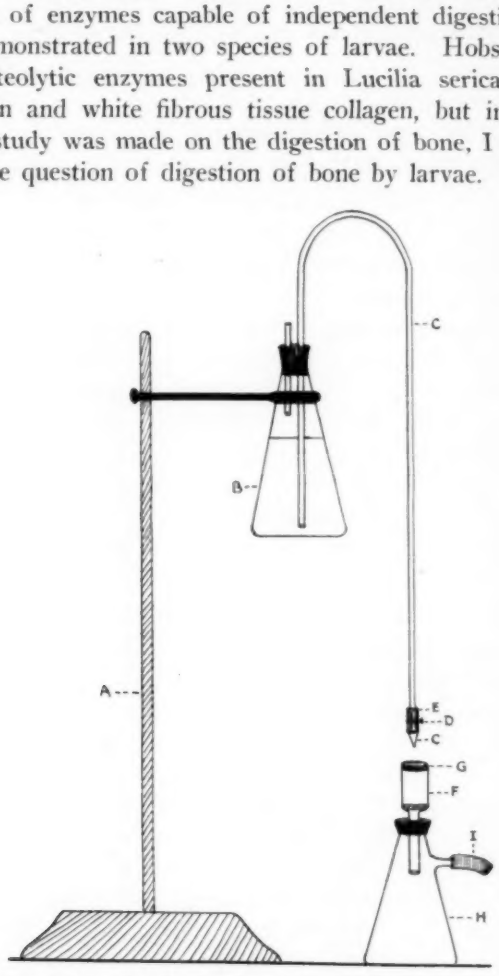

Fig. 1.—Diagrammatic sketch showing sintered filter and attachment of flask: *A*, stand; *B*, flask for water; *C*, glass tubing; *D*, screw clamp; *E*, rubber tubing; *F*, sintered filter; *G*, gauze covering filter; *H*, suction flask, and *I*, rubber tubing to vacuum.

PRELIMINARY PREPARATIONS

Extraction of Enzymes from the Excreta of Larvae.—The methods for the extraction of enzymes are taken from those used by Wigglesworth and later by Hobson.

The maggots used in this work were pure strains of Phormia regina. Attempts were made to raise larvae on Baer's medium, under sterile as well as under nonsterile conditions. Maggots readily reached full growth on this food, but from 50 to 60 per cent of the larvae were dead at the end of forty-eight hours. Similar

results were obtained by raising the maggots on calf and hog brains. Extremely rapid liquefaction occurred in these mediums, and it was felt that toxic metabolic products were produced which caused destruction of the larvae. Beef, however, was found to be a very favorable medium for raising larvae under nonsterile conditions. Single strips of fresh lean beef, about 4 by 3 by 2 inches (10 by 7.5 by 0.5 cm.), were placed in a series of urine flasks. Approximately 100 maggots diluted with 2 cc. of distilled water were added to each flask. The mouths of the bottles were then plugged with cotton and the larvae incubated at 37 C. for forty-eight hours. At the end of this time the maggots were washed from the meats and bottles, distilled water being used, into a filter covered with a 60 mesh wire screen. Washings were continued until the filtrate was returned clear. The maggots were then placed over a sintered filter (fig. 1) covered with several layers of gauze. About 800 maggots were used during each period of extraction. This filter was then connected to a vacuum suction tube passing into the incubator. The suction, by disturbing the maggots, stimulated activity, whereas its absence admitted abnormal pupation. Distilled water was slowly dripped over the larvae and collected in the suction flask. An average of 30 cc. was collected during a period of five hours. The excreta consisted of a dark brown liquid suspension having an average hydrogen ion concentration of p_H 8.

Preparation of Bone.—Bone from human ribs was prepared by being scraped free from foreign tissues. Two preparations were made, one consisting of firm compact cortical bone and the other of finely ground bone. The preparations were completely dehydrated, well washed and again dehydrated. The cortical portions were made up into strips weighing 25 mg. each.

Controls.—The excreta were divided into two portions. One was left unaltered, while the other was heated over a water bath at 100 C. for five minutes. The first will be designated as unchanged excreta; the second, as heated excreta.

DIGESTIVE ACTION OF LARVAL EXCRETA

To 1 cc. portions of the unchanged excreta were added fixed amounts of bone. The cortical portions, as described, weighed 25 mg. each; 10 mg. of ground bone was used in each of these tests. Two controls were used; one consisted of heated excreta and bone and the other of unchanged excreta, to which no material was added. Small portions of thymol were added to all. Digestion was determined by loss of weight and increase in formaldehyde titrations. When ground bone was used, final determinations were calculated by the increase in formaldehyde titrations alone. All results were expressed in milligrams or fractions thereof or in cubic centimeters of hundredth-normal sodium hydroxide. All preparations were incubated at 37 C. for twenty-four hours. Digestion of ground bone occurred, as was evidenced by increase in formaldehyde titrations. In all cases, when whole cortical bone was used no changes resulted (table 1).

It is evident from these findings that the excreta of the larvae of Phormia regina contain an enzyme capable of digesting the organic portion of bone. Further studies, therefore, were made on ossein prepared from human ribs. All foreign tissue and the cancellous portion

of the bone were removed. The remaining cortical portions of the bone were then treated with 10 per cent hydrochloric acid for several days, well washed in distilled water, cut into strips and dehydrated. The average weight of the strips in a completely dehydrated state was 25 mg. A preliminary study was then made of the digestion of ossein by the excreta, and final calculations were determined by loss of weight and formaldehyde titrations. Controls were used as described in the experiments with whole bone. All mixtures were incubated at 37 C.

TABLE 1.—*Results of Experiments with Cortical and Ground Bone*

	Loss of Weight, Mg.	Final Titrations, Cc. of Hundredth-Normal NaOH
Experiment 1		
Cortical bone plus unchanged excreta	0	0
Cortical bone plus heated excreta	0	0
Ground bone plus unchanged excreta	—	0.4
Ground bone plus heated excreta	—	0
Unchanged excreta (control)	—	—
Experiment 2		
Cortical bone plus unchanged excreta	0	0
Cortical bone plus heated excreta	0	0
Ground bone plus unchanged excreta	—	0.32
Ground bone plus heated excreta	—	0
Unchanged excreta (control)	—	—
Experiment 3		
Cortical bone plus unchanged excreta	0	0
Cortical bone plus heated excreta	0	0
Ground bone plus unchanged excreta	—	0.34
Ground bone plus heated excreta	—	0
Unchanged excreta (control)	—	—
Experiment 4		
Cortical bone plus unchanged excreta	0	0
Cortical bone plus heated excreta	0	0
Ground bone plus unchanged excreta	—	0.46
Ground bone plus heated excreta	—	0
Unchanged excreta (control)	—	—
Experiment 5		
Cortical bone plus unchanged excreta	0	0
Cortical bone plus heated excreta	0	0
Ground bone plus unchanged excreta	—	0.36
Ground bone plus heated excreta	—	0
Unchanged excreta (control)	—	—

for twenty-four hours. Both decrease in weight and increase in formaldehyde titration occurred, showing digestion of ossein. All the controls gave negative results. The work was repeated, and the calculations are given in table 2.

Ssadikow (1927) isolated a collagenase from ox pancreas. He showed that kaolin absorbed the collagenase, while charcoal had no effect. Hobson (1931) repeated this work with maggots. He prepared white fibrous tissue collagen from catgut and treated it with the excreta of Lucilia sericata. After a series of experiments, he concluded that the enzyme acting on collagen, a substance similar to commercial gelatin, was entirely different from the one that digested gelatin. Bone collagen, according to Richard and Gies, possesses a chemical formula which differs slightly from that of tendon collagen; hence, it was felt that

the enzyme digesting bone collagen might prove to be specific for this substance only, and tests were instituted.

Since the determination of a collagenase depends on comparative study with other proteolytic enzymes and in view of the fact that no previous work had demonstrated the presence of such enzymes in the larvae of Phormia regina, it was found necessary to make preliminary studies.

Collagen was prepared from catgut, well washed and dehydrated. Commercial gelatin in a 5 per cent solution was used for simple proteolytic determinations. About 25 mg. of catgut and 1 cc. portions of gelatin were added to 1 cc. quantities of excreta. Controls, as previ-

TABLE 2.—*Results of Experiments with Ossein*

	Loss of Weight, Mg.	Increase in Formaldehyde Titration, Cc. of Hundredth-Normal NaOH
Experiment 1		
Ossein plus unchanged excreta	3.1	0.56
Ossein plus heated excreta	0	0
Unchanged excreta (control)	—	—
Experiment 2		
Ossein plus unchanged excreta	2.8	0.4
Ossein plus heated excreta	0	0
Unchanged excreta (control)	—	0
Experiment 3		
Ossein plus unchanged excreta	3.2	0.42
Ossein plus heated excreta	0	0
Unchanged excreta (control)	—	—
Experiment 4		
Ossein plus unchanged excreta	2.2	0.36
Ossein plus heated excreta	0	0
Unchanged excreta (control)	—	—
Experiment 5		
Ossein plus unchanged excreta	3.5	0.52
Ossein plus heated excreta	0	0
Unchanged excreta (control)	—	—

ously described, were used, and thymol was added to all. The digestion of catgut was determined by loss of weight and by formaldehyde titrations, while the digestion of gelatin was determined by formaldehyde titrations alone. Repeated experiments showed the presence of proteolytic enzymes which were capable of digesting both catgut and gelatin.

COMPARATIVE STUDY OF PROTEOLYTIC ENZYMES AND ATTEMPT TO EXTRACT A COLLAGENASE SPECIFIC FOR BONE

The bone collagen (ossein) used in this work was subjected to 25 per cent loss of weight by preliminary digestion so as to eliminate osseoalbuminoid, osseomucoid and the small portions of gelatin that might have been converted by previous contact with hydrochloric acid. In the same manner catgut was also subjected to predigestion.

Excreta were collected in the usual manner, and 6 cc. portions were treated, respectively, with 1 Gm. of animal charcoal and 1 Gm. of

kaolin. The tubes were shaken at frequent intervals for one-half hour and the contents filtered. To 1 cc. portions of the treated excreta were added catgut, bone collagen and 1 cc. portions of 5 per cent gelatin. Similar quantities were added to 1 cc. portions of unchanged excreta and heated controls. Portions of unchanged excreta (1 cc.) to which no material was added were used as basic controls for formaldehyde titrations. Thymol was added in each case. Incubations were carried out for forty-eight hours at 37 C. Digestion was determined by loss of weight when catgut or bone collagen was concerned, while formaldehyde titrations were used to determine the digestion of gelatin.

TABLE 3.—*Results of Experiments with Charcoal and Kaolin*

	Catgut Digested; Loss of Weight, Mg.	Bone Collagen Digested; Loss of Weight, Mg.	Gelatin Digested; Increase in Formaldehyde Titrations, Cc.
Preparation 1			
1. Excreta unchanged	5.5	3.0	1.4
2. Excreta treated with charcoal	3.1	1.5	0.9
3. Excreta treated with kaolin...	3.1	1.6	0.8
4. Heated controls	0	0	0
Preparation 2			
1. Excreta unchanged	4.2	3.5	1.6
2. Excreta treated with charcoal	2.1	2.4	1.4
3. Excreta treated with kaolin...	4.2	3.2	1.4
4. Heated controls	0	0	0
Preparation 3			
1. Excreta unchanged	3.4	3.15	1.2
2. Excreta treated with charcoal	2.9	3.05	0.8
3. Excreta treated with kaolin...	2.0	2.9	0.9
4. Heated controls	0	0	0
Preparation 4			
1. Excreta unchanged	3.3	3.4	1.4
2. Excreta treated with charcoal	2.85	3.0	1.0
3. Excreta treated with kaolin...	3.1	3.7	0.8
4. Heated controls	0	0	0
Preparation 5			
1. Excreta unchanged	3.2	3.1	1.8
2. Excreta treated with charcoal	2.8	2.5	1.0
3. Excreta treated with kaolin...	1.6	2.4	1.2
4. Heated controls	0	0	0

Careful study of the findings shown in table 3 will prove absorption of enzymes by kaolin and charcoal. These absorptive changes are present when catgut, bone collagen or gelatin is used. Furthermore, there is no evidence of specific absorption. Ssadikow (1927) found that kaolin completely absorbed the enzyme capable of digesting collagen, and further found that no changes occurred when this enzyme was treated with charcoal. It is therefore evident that the presence of a separate enzyme capable of digesting either catgut or bone collagen was not demonstrated. The changes found in this work also differ from those described by Hobson. From the findings it may be concluded that the proteolytic enzymes extracted from the excreta of Phormia regina are capable of digesting collagen, ossein and gelatin and are in all probability the same specific enzymes.

ORIGIN OF THE PROTEOLYTIC ENZYMES

Action of Emulsions of Intestinal Tracts and Salivary Glands on Bone Collagen.—The intestinal tracts and salivary glands of 80 fed larvae were isolated with the aid of a dissecting microscope. Each material was well emulsified and diluted to 10 cc. with 50 per cent glycerin. Portions containing 5 cc. of both the intestinal and the salivary emulsion were heated over a water bath at 100 C. for five minutes. The emulsions were divided into 1 cc. portions, and thymol was added. Human bone collagen was added to each, and incubations were carried on for twenty-four hours at 37 C. The collagen was then removed, well washed, dehydrated and reweighed. Digestion was determined by loss of weight as compared with absence of change in the heated con-

TABLE 4.—*Experiments with Intestinal and Salivary Emulsions*

	Mg. Collagen Digested
Experiment 1	
Bone collagen plus unchanged intestinal emulsion	3.9
Bone collagen plus heated intestinal emulsion	0
Experiment 2	
Bone collagen plus unchanged intestinal emulsion	3.1
Bone collagen plus heated intestinal emulsion	0
Experiment 3	
Bone collagen plus unchanged intestinal emulsion	3.7
Bone collagen plus heated intestinal emulsion	0
Experiment 4	
Bone collagen plus unchanged intestinal emulsion	4.2
Bone collagen plus heated intestinal emulsion	0
Experiment 5	
Bone collagen plus unchanged intestinal emulsion	3.1
Bone collagen plus heated intestinal emulsion	0

trols. Collagen was digested by the intestinal emulsions, but no changes were present in any of the gland preparations (table 4).

It is evident, therefore, that the enzymes found in the excreta are passed from the intestinal tracts of the larvae. It is not assumed, however, that the negative action of the gland emulsions definitely eliminates these tissues as the possible source of origin of proteolytic enzymes. There are many factors to be weighed, and in view of the limited literature and the differences in opinion concerning the salivary glands, it will be necessary that this problem be investigated further before a definite conclusion can be drawn.

The findings in table 4 are of further interest when compared with those of Hobson on the larvae of Lucilia sericata. He found that the collagenase was not present in emulsions made from the intestinal tracts of fed larvae, and further that the collagenase in intestinal emulsions of starved larvae was present only to a moderate degree when compared with the action of excreta. A comparative study of tables 4 and 2

shows that intestinal emulsions of fed larvae are more capable of digesting ossein than similar quantities of excreta. Since Hobson used catgut in his experiments, we proceeded to investigate the action of intestinal emulsions of fed larvae (Phormia regina) on this substance. The emulsions were found to digest catgut equally well and, when compared with the excreta, showed greater activity.

Action of Bacteria on Bone Collagen.—Since the larvae used for the preceding work were raised on nonsterile mediums, it seemed necessary to consider the possibility that bacteria might play some part in the process of digestion. Repeated cultures and smears made directly from intestinal contents always showed the presence of a gram-negative bacillus and a gram-negative coccus. The bacillus was of the proteus group while the coccus proved to be M. flavus-liquefaciens, both of which had been demonstrated by previous workers. At no time could other organisms be isolated, other than specific bacteria, when these were inoculated on sterile maggot mediums.

Since all maggots used in this work were removed from nonsterile mediums after forty-eight hours' growth, cultures of these bacteria were grown on agar slants for two days and then suspended in physiologic solution of sodium chloride. To 1 cc. portions of forty-eight hour suspensions bone collagen was added. Controls of physiologic solution of sodium chloride were used. Since thymol had been used in each previous experiment, small amounts were added to all the portions. No digestion of bone collagen occurred. In order to check these results, bone collagen was treated with alcohol for one week, well washed with sterile water and then placed in a sterile medium containing feeding larvae. Examination after forty-eight hours showed digestion of bone collagen. Bacteria, therefore, played no rôle in the preceding experiments.

STABILITY OF THE ENZYME

A brief study was made to determine the stability of the enzyme. Intestinal emulsions were prepared, eight intestines being used for each cubic centimeter of saline solution. Equal portions of glycerin were added to half of the aliquots and thymol to all. The emulsions were

TABLE 5.—*Experiments to Determine Stability of the Enzyme*

	Mg. of Bone Collagen Digested
Bone collagen plus excreta plus thymol after 24 hours	2.8
Bone collagen plus excreta plus thymol plus glycerin after 24 hours	3.2
Bone collagen plus excreta plus thymol after 48 hours	2.2
Bone collagen plus excreta plus thymol plus glycerin after 48 hours	3.1
Bone collagen plus excreta plus thymol after 72 hours	1.9
Bone collagen plus excreta plus thymol plus glycerin after 72 hours	3.1
Bone collagen plus excreta plus thymol after 1 week	1.75
Bone collagen plus excreta plus thymol plus glycerin after 1 week	2.9

incubated, and after twenty-four, forty-eight and seventy-two hours and one week bone collagen was added to both glycerin and plain emulsions. Further incubations were then carried out for forty-eight hours at 37 C. The results are given in table 5.

A study of table 5 shows that the enzyme possesses a fair amount of stability. Guyénot (1907) showed that maggots were capable of ingesting only microscopic particles, and it would therefore appear that stability of enzymes would be a necessity for the existence of larval life.

PROTEOLYTIC ACTIVITY AT VARIOUS HYDROGEN ION CONCENTRATIONS

It was felt to be of value and of interest to determine the concentration at which proteolytic activity reached a maximum. Emulsions were made with five intestinal tracts to each cubic centimeter of buffer solution at various concentrations as shown in figure 2. These emulsions were corrected when necessary, and equal portions of ossein were added to each. The results are presented in figure 2.

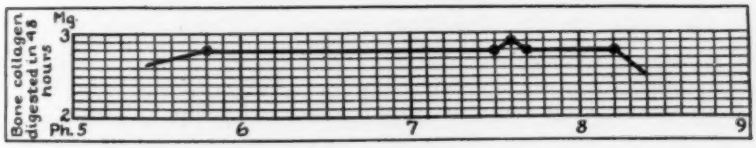

Fig. 2.—Chart showing proteolytic activity at various hydrogen ion concentrations.

The findings failed to reveal an appreciable point of maximum activity, but showed a rather wide range with virtually no variation. At p_H 7.5 there was an increase in the digestion of collagen of 0.1 mg., while below p_H 5.8 and above p_H 8.2 the activity decreased. This wide range apparently would permit the larvae to adapt themselves to an average medium.

SUMMARY OF OBSERVATIONS IN FOREGOING SECTIONS, WITH COMMENT

The intestines of the larvae of Phormia regina excrete a proteolytic enzyme capable of digesting bone. The digestion occurs essentially on ossein, the organic portion of the bone. No attempt was made to determine the ultimate fate of the inorganic salts; since this matter would involve an extensive investigation, the subject was left open for further research. The enzyme, which can also be extracted from the excreta of the larvae, shows fair stability and is capable of maximum activity over a wide range. Digestion of gelatin and collagen derived from white fibrous tissue has also been demonstrated, but a specific enzyme for each of the substances could not be found.

It is of interest to note that Shinoda (1928) showed digestion of collagen by the gastric juice of the crawfish (Astacus) but felt that, with the present knowledge of enzymes, an attempt to extract a specific agent was not feasible. He, too, found that the activity of the enzyme occurred over a wide range with little evidence of a maximum point of digestion.

RELATIONSHIP OF MAGGOTS TO BACTERIA

For years it was felt that bacteria played an essential part in larval digestion. Baumberger (1919) stated that bacteria were an important source of food, while Portier (1919) considered them a source of vitamins for maggots. My previous study of digestion obviates the necessity for any further preliminary review of the literature other than a consideration of several factors. It has been proved that bacteria are not necessary to the growth of larvae. Duncan (1926) and other workers have demonstrated bacterial destruction by the intestines of maggots. Whether maggots are capable of destroying bacteria by virtue of immunity or by digestion is open for consideration, since no specific evidence has thus far been given relating to this subject. Livingston (1932) felt that an active principle was present which was capable of destroying bacteria, and, furthermore, he believed that this active substance could be extracted by making emulsions of mashed maggots. No experimental evidence was given other than the ingestion of bacteria by larvae and the clinical evidence of cures. The question of the relationship of maggots to bacteria is therefore open for further investigation.

Procedure.—Maggots were cultivated by aseptic means, the Baer beef, liver and yeast medium being employed. About 200 maggots were emulsified with physiologic solution of sodium chloride to make a liquid suspension. Twenty-four hour growths of Staphylococcus aureus, Pneumococcus, the typhoid bacillus, Bacillus proteus and Micrococcus flavus-liquefaciens were suspended in physiologic solution of sodium chloride, very dilute suspensions being made. The staphylococcus was obtained from the wound of an operation for osteomyelitis, while B. proteus and the micrococcus were taken from an intestinal smear of maggots. Dilutions as high as 1:16 were made of the maggot emulsions. The usual routine bactericidal tests were performed with each type of bacterium mentioned, a saline control being used in every case. In each group 1 cc. of emulsion was mixed with 0.5 cc. of bacterial suspension, incubated at 37 C. for three hours, plated on agar and incubated for twenty-four hours, and the colonies were then counted. This work was repeated with sterile maggots raised on Baer's medium which had been inoculated with each of the organisms described, i. e., Staphylococcus in flask 1, Pneumococcus in flask 2, etc.

Results of both groups of experiments are given in tables 6 to 10.

A study of the results shows that emulsions of maggots are not bactericidal in action, but on the contrary favor bacterial growth.

TABLE 6.—*Bactericidal Tests with Emulsions of Maggots and Staph. Aureus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. S. aureus suspension	1,280	1,620
Diluted 1:2 plus 0.5 cc. S. aureus suspension	848	1,360
Diluted 1:4 plus 0.5 cc. S. aureus suspension	800	820
Diluted 1:8 plus 0.5 cc. S. aureus suspension	496	670
Diluted 1:16 plus 0.5 cc. S. aureus suspension	380	500
1 cc. physiologic solution of sodium chloride plus 0.5 cc. S. aureus suspension	132	236
Experiment 2		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. S. aureus suspension	1,440	1,280
Diluted 1:2 plus 0.5 cc. S. aureus suspension	644	750
Diluted 1:4 plus 0.5 cc. S. aureus suspension	770	648
Diluted 1:8 plus 0.5 cc. S. aureus suspension	416	307
Diluted 1:16 plus 0.5 cc. S. aureus suspension	65	120
1 cc. physiologic solution of sodium chloride plus 0.5 cc. S. aureus suspension	84	96
Experiment 3		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. S. aureus suspension	1,318	1,414
Diluted 1:2 plus 0.5 cc. S. aureus suspension	890	840
Diluted 1:4 plus 0.5 cc. S. aureus suspension	480	632
Diluted 1:8 plus 0.5 cc. S. aureus suspension	328	460
Diluted 1:16 plus 0.5 cc. S. aureus suspension	214	310
1 cc. physiologic solution of sodium chloride plus 0.5 cc. S. aureus suspension	57	84

TABLE 7.—*Bactericidal Tests with Emulsions of Maggots and B. Typhosus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. B. typhosus suspension	1,136	1,158
Diluted 1:2 plus 0.5 cc. B. typhosus suspension	794	864
Diluted 1:4 plus 0.5 cc. B. typhosus suspension	560	619
Diluted 1:8 plus 0.5 cc. B. typhosus suspension	500	420
Diluted 1:16 plus 0.5 cc. B. typhosus suspension	370	314
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	122	108
Experiment 2		
1 cc. maggot emulsion		
Undiluted plus 0.5 cc. B. typhosus suspension	690	940
Diluted 1:2 plus 0.5 cc. B. typhosus suspension	585	796
Diluted 1:4 plus 0.5 cc. B. typhosus suspension	480	598
Diluted 1:8 plus 0.5 cc. B. typhosus suspension	328	320
Diluted 1:16 plus 0.5 cc. B. typhosus suspension	214	116
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	57	72
Experiment 3		
Undiluted plus 0.5 cc. B. typhosus suspension	898	762
Diluted 1:2 plus 0.5 cc. B. typhosus suspension	772	372
Diluted 1:4 plus 0.5 cc. B. typhosus suspension	567	459
Diluted 1:8 plus 0.5 cc. B. typhosus suspension	328	274
Diluted 1:16 plus 0.5 cc. B. typhosus suspension	240	116
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	96	84

TABLE 8.—*Bactericidal Tests with Suspensions of Maggots and Pneumococcus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. pneumococcus suspension	630	670
Diluted 1:2 plus 0.5 cc. pneumococcus suspension	510	420
Diluted 1:4 plus 0.5 cc. pneumococcus suspension	379	400
Diluted 1:8 plus 0.5 cc. pneumococcus suspension	160	182
Diluted 1:16 plus 0.5 cc. pneumococcus suspension	46	94
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	58	84
Experiment 2		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. pneumococcus suspension	590	520
Diluted 1:2 plus 0.5 cc. pneumococcus suspension	360	412
Diluted 1:4 plus 0.5 cc. pneumococcus suspension	270	300
Diluted 1:8 plus 0.5 cc. pneumococcus suspension	200	168
Diluted 1:16 plus 0.5 cc. pneumococcus suspension	102	96
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	48	50
Experiment 3		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. pneumococcus suspension	412	390
Diluted 1:2 plus 0.5 cc. pneumococcus suspension	290	248
Diluted 1:4 plus 0.5 cc. pneumococcus suspension	200	172
Diluted 1:8 plus 0.5 cc. pneumococcus suspension	168	106
Diluted 1:16 plus 0.5 cc. pneumococcus suspension	38	32
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	86	80

TABLE 9.—*Bactericidal Tests with Suspensions of Maggots and B. Proteus*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. B. proteus suspension	1,680	1,470
Diluted 1:2 plus 0.5 cc. B. proteus suspension	1,292	1,264
Diluted 1:4 plus 0.5 cc. B. proteus suspension	730	692
Diluted 1:8 plus 0.5 cc. B. proteus suspension	414	274
Diluted 1:16 plus 0.5 cc. B. proteus suspension	196	196
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	104	176
Experiment 2		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. B. proteus suspension	1,388	1,414
Diluted 1:2 plus 0.5 cc. B. proteus suspension	694	1,002
Diluted 1:4 plus 0.5 cc. B. proteus suspension	710	685
Diluted 1:8 plus 0.5 cc. B. proteus suspension	390	329
Diluted 1:16 plus 0.5 cc. B. proteus suspension	176	206
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	172	183
Experiment 3		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. B. proteus suspension	1,880	1,666
Diluted 1:2 plus 0.5 cc. B. proteus suspension	1,438	749
Diluted 1:4 plus 0.5 cc. B. proteus suspension	1,096	586
Diluted 1:8 plus 0.5 cc. B. proteus suspension	648	484
Diluted 1:16 plus 0.5 cc. B. proteus suspension	580	320
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	320	192

A preliminary study was now made of bacteria found in the intestinal tracts of the larvae of Phormia regina. B. proteus and M. flavus-liquefaciens, which have already been described, could be seen in abundance in intestinal smears. Grown maggots were placed on a sintered filter and covered with gauze. The larvae were washed with a slow stream of water which was continuously removed by a vacuum suction apparatus connected to a flask. In this manner the larvae were kept moist and active. Starvation was continued for a week, and each day the maggots that had survived the ordeal were

TABLE 10.—*Bactericidal Tests with Suspensions of Maggots and M. Flavus Liquefaciens*

	Number of Colonies After 24 Hours of Incubation	
	Filtered Emulsion	Nonsterile Emulsion
Experiment 1		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension...	1,242	1,358
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension..	868	846
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	588	592
Diluted 1:8 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	346	464
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	244	322
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	226	245
Experiment 2		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension...	1,300	1,106
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	864	1,650
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	792	549
Diluted 1:8 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	506	364
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	375	298
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	162	184
Experiment 3		
1 cc. maggot suspension		
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension...	870	1,012
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	644	804
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	328	658
Diluted 1:8 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension.	204	436
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	162	208
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	122	188

removed. At intervals, examinations were made of intestinal smears, but no gross evidence of decrease in bacteria could be noted. Further study was then made by emulsifying intestinal tracts which had been dissected from the maggots. About ten intestinal tracts were used to each cubic centimeter of physiologic solution of sodium chloride, and the solution was filtered through a Mandler filter. Bactericidal tests were made, the technic and organisms used being the same as those previously described. The results of these experiments were negative. Representative tests are recorded in table 11.

Further studies were then made, consisting of agglutination tests, both microscopic and macroscopic. Observations were also made for lytic changes. Emulsions were prepared of whole sterile maggots and contaminated maggots as described, i. e., maggots fed in mediums inocu-

lated with pure strains of Staphylococcus, Pneumococcus and other organisms, and emulsions of intestines. The emulsion of whole maggots was prepared by mashing 200 larvae and diluting with physiologic solution of sodium chloride, while ten intestinal tracts to each cubic centimeter of saline solution were used in the second preparation.

TABLE 11.—*Results of Bactericidal Tests with Emulsions of Larval Intestines and Bacteria Found in Larval Intestinal Tracts*

	Number of Colonies After 24 Hours' Incubation
Experiment 1	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. Staphylococcus aureus suspension	1,330
Diluted 1:2 plus 0.5 cc. Staphylococcus aureus suspension	1,012
Diluted 1:4 plus 0.5 cc. Staphylococcus aureus suspension	860
Diluted 1:8 plus 0.5 cc. Staphylococcus aureus suspension	488
Diluted 1:16 plus 0.5 cc. Staphylococcus aureus suspension	360
1 cc. physiologic solution of sodium chloride	166
Experiment 2	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. pneumococcus suspension	1,160
Diluted 1:2 plus 0.5 cc. pneumococcus suspension	876
Diluted 1:4 plus 0.5 cc. pneumococcus suspension	648
Diluted 1:8 plus 0.5 cc. pneumococcus suspension	412
Diluted 1:16 plus 0.5 cc. pneumococcus suspension	220
1 cc. physiologic solution of sodium chloride plus 0.5 cc. pneumococcus suspension	176
Experiment 3	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. B. typhosus suspension	940
Diluted 1:2 plus 0.5 cc. B. typhosus suspension	866
Diluted 1:4 plus 0.5 cc. B. typhosus suspension	572
Diluted 1:8 plus 0.5 cc. B. typhosus suspension	268
Diluted 1:16 plus 0.5 cc. B. typhosus suspension	138
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. typhosus suspension	100
Experiment 4	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. B. proteus suspension	1,124
Diluted 1:2 plus 0.5 cc. B. proteus suspension	910
Diluted 1:4 plus 0.5 cc. B. proteus suspension	880
Diluted 1:8 plus 0.5 cc. B. proteus suspension	574
Diluted 1:16 plus 0.5 cc. B. proteus suspension	254
1 cc. physiologic solution of sodium chloride plus 0.5 cc. B. proteus suspension	238
Experiment 5	
1 cc. intestinal emulsion	
Undiluted plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	728
Diluted 1:2 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	712
Diluted 1:4 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	436
Diluted 1:8 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	294
Diluted 1:16 plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	188
1 cc. physiologic solution of sodium chloride plus 0.5 cc. Micrococcus flavus-liquefaciens suspension	87

All emulsions were filtered through a Mandler filter. Portions (1 cc.) of very dilute suspensions of twenty-four hour bacterial growths were added to the emulsions and incubated for several hours at 37 C. Microscopic agglutination tests were made, 1 loopful of emulsion and 1 loopful of bacterial suspension being used. Observations were made for several hours, during which time the hollow ground slide suspensions were incubated as described. There was no evidence of definite agglutination or lysis (table 12).

TABLE 12.—*Tests for Agglutination and for Lysis of Bacteria by Emulsions of Whole Maggots Contaminated and Uncontaminated and by Emul-*

TABLE 12.—*Tests for Agglutination and for Lysis of Bacteria by Emulsions of Whole Maggots Contaminated and Uncontaminated and by Emulsions of Their Intestines*

	Staphylococcus Aureus			Pneumococcus			B. Typhosus			B. Proteus			M. Flavus-Liquefaciens		
	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis	Gross Agglutination	Microscopic Agglutination	Lysis
(1) Whole maggot emulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Whole maggot emulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Whole maggot emulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Whole maggot emulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Whole maggot emulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(2) Whole maggot emulsion treated with Staph. aureus	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
Same	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
Same	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
Same	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
Same	0	0	0	—	—	—	—	—	—	—	—	—	—	—	—
(3) Whole maggot emulsion treated with pneumococcus	—	—	—	0	0	0	—	—	—	—	—	—	—	—	—
Same	—	—	—	0	0	0	—	—	—	—	—	—	—	—	—
Same	—	—	—	0	0	0	—	—	—	—	—	—	—	—	—
Same	—	—	—	0	0	0	—	—	—	—	—	—	—	—	—
Same	—	—	—	0	0	0	—	—	—	—	—	—	—	—	—
(4) Whole maggot emulsion treated with B. typhosus	—	—	—	—	—	—	0	0	0	—	—	—	—	—	—
Same	—	—	—	—	—	—	0	0	0	—	—	—	—	—	—
Same	—	—	—	—	—	—	0	0	0	—	—	—	—	—	—
Same	—	—	—	—	—	—	0	0	0	—	—	—	—	—	—
Same	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(5) Whole maggot emulsion treated with B. proteus	—	—	—	—	—	—	—	—	—	0	0	0	—	—	—
Same	—	—	—	—	—	—	—	—	—	0	0	0	—	—	—
Same	—	—	—	—	—	—	—	—	—	0	0	0	—	—	—
Same	—	—	—	—	—	—	—	—	—	0	0	0	—	—	—
Same	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(6) Whole maggot emulsion treated with M. flavus-liquefaciens	—	—	—	—	—	—	—	—	—	—	—	—	0	0	0
Same	—	—	—	—	—	—	—	—	—	—	—	—	0	0	0
Same	—	—	—	—	—	—	—	—	—	—	—	—	0	0	0
Same	—	—	—	—	—	—	—	—	—	—	—	—	0	0	0
Same	—	—	—	—	—	—	—	—	—	—	—	—	0	0	0
(7) Intestinal emulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Same	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Same	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Same	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Same	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

The final study was devoted to the possibility of digestion of bacteria by larvae. Emulsions were made of ten intestinal tracts and 1 cc. of physiologic solution of sodium chloride. Dilute saline suspensions were

TABLE 13.—*Tests for Digestion of Bacteria by Emulsions of Larval Intestines*

		Increase in Formaldehyde Titration, Cc. Hundredth-Normal NaOH
Experiment 1		
(1)	1 cc. unchanged intestinal emulsion plus 1 cc. S. aureus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. S. aureus suspension	0
	1 cc. unchanged control	—
(2)	1 cc. unchanged intestinal emulsion plus 1 cc. S. aureus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. S. aureus suspension	0
	1 cc. unchanged control	—
(3)	1 cc. unchanged intestinal emulsion plus 1 cc. S. aureus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. S. aureus suspension	0
	1 cc. unchanged control	—
Experiment 2		
(1)	1 cc. unchanged intestinal emulsion plus 1 cc. B. typhosus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. B. typhosus suspension	0
	1 cc. unchanged control	—
(2)	1 cc. unchanged intestinal emulsion plus 1 cc. B. typhosus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. B. typhosus suspension	0
	1 cc. unchanged control	—
(3)	1 cc. unchanged intestinal emulsion plus 1 cc. B. typhosus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. B. typhosus suspension	0
	1 cc. unchanged control	—
Experiment 3		
(1)	1 cc. unchanged intestinal emulsion plus 1 cc. B. proteus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. B. proteus suspension	0
	1 cc. unchanged control	—
(2)	1 cc. unchanged intestinal emulsion plus 1 cc. B. proteus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. B. proteus suspension	0
	1 cc. unchanged control	—
(3)	1 cc. unchanged intestinal emulsion plus 1 cc. B. proteus suspension	0
	1 cc. heated intestinal emulsion plus 1 cc. B. proteus suspension	0
	1 cc. unchanged control	—
Experiment 4		
(1)	1 cc. unchanged intestinal emulsion plus 1 cc. M. flavus-liquefaciens susp...	0
	1 cc. heated intestinal emulsion plus 1 cc. M. flavus-liquefaciens suspension	0
	1 cc. unchanged control	—
(2)	1 cc. unchanged intestinal emulsion plus 1 cc. M. flavus-liquefaciens susp...	0
	1 cc. heated intestinal emulsion plus 1 cc. M. flavus-liquefaciens suspension	0
	1 cc. unchanged control	—
(3)	1 cc. unchanged intestinal emulsion plus 1 cc. M. flavus-liquefaciens susp...	0
	1 cc. heated intestinal emulsion plus 1 cc. M. flavus-liquefaciens suspension	0
	1 cc. unchanged control	—
Experiment 5		
(1)	1 cc. unchanged intestinal emulsion plus 1 cc. pneumococcus suspension....	0
	1 cc. heated intestinal emulsion plus 1 cc. pneumococcus suspension.....	0
	1 cc. unchanged control	—
(2)	1 cc. unchanged intestinal emulsion plus 1 cc. pneumococcus suspension....	0
	1 cc. heated intestinal emulsion plus 1 cc. pneumococcus suspension.....	0
	1 cc. unchanged control	—
(3)	1 cc. unchanged intestinal emulsion plus 1 cc. pneumococcus suspension....	0
	1 cc. heated intestinal emulsion plus 1 cc. pneumococcus suspension.....	0
	1 cc. unchanged control	—

made of Staph. aureus, the typhoid bacillus, Pneumococcus, B. proteus and M. flavus-liquefaciens. Quantities of 1 cc. of each were added to equal portions of intestinal emulsions, and a preliminary study of bacterial counting was attempted. No changes were noted, and the results were

not considered sufficiently accurate to record. Heavy twenty-four hour suspensions of bacteria in physiologic solution of sodium chloride were then added to intestinal emulsions, 1 cc. portions of each being employed. Thymol was added in each case, and controls as described were run in series. Digestion was determined by increase in formaldehyde titrations. All results were negative (table 13).

SUMMARY OF OBSERVATIONS IN FOREGOING SECTION

The work failed to reveal any bactericidal action, agglutination, lysis or digestion of bacteria and does not confirm the claims of previous workers.

CONCLUSIONS

1. The intestines and excreta of the larvae of Phormia regina contain proteolytic enzymes capable of digesting ossein, white fibrous tissue collagen and gelatin.

2. No specificity of enzymes could be demonstrated.

3. The enzymes are fairly stable, and the activity extends over a wide range, the optimum being from p_H 5.8 to p_H 8.2.

4. No bactericidal action, agglutination, lysis or digestion of bacteria could be detected.

Dr. Alfred Ullman, surgeon-in-chief, made available the research fund and laboratories of the Sinai Hospital. The Lederle Laboratories, Inc., donated maggots throughout this work. Dr. Edward F. Roberts, assistant director, gave his cooperation.

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FIFTY-SECOND REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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(Concluded from page 424)

MISCELLANEOUS

Degeneration of Rib Cartilage.—Following Trauma: Bauer[25] reported a rare form of chondromalacia of the cartilages of the fourth and fifth ribs on the right side following a severe injury to this region. Because of pain, these cartilages were removed with complete relief from symptoms. Examination of the cartilage that was removed showed necrosis and degeneration which, the author believed, were the result of local vascular damage. Five similar lesions in the costal cartilages had been reported in the literature.

Morphologic Changes in the Wrist Joint After Removal of the Carpal Semilunar Bone.—Dietrich[26] studied the changes in the wrist joint after extirpation of the carpal semilunar bone for osteoporosis in 11 cases. He observed an ulnar displacement of the scaphoid and a narrowed articulation with the radius. The carpal bones had a decreased length in the axis of the limb, and the capitatum was

25. Bauer, C. D.: Ztschr. f. Chir. **239**:733, 1932.
26. Dietrich, H.: Arch. f. klin. Chir. **174**:146, 1933.

in a deeper position. External rotation and abduction were decreased. When only partial extirpation had been performed, partial regeneration often occurred.

Bipartite Carpal Navicular Bone.—Reporting a case found post mortem, Boyd [27] reconsidered the question of bipartite carpal navicular bone. The points differentiating this from a fracture of the navicular bone were taken to be: (1) absence of history of injury; (2) meagerness of physical signs; (3) roentgenographic appearance (in the congenital condition the cortex was uniform around the segments of the bone, while in the traumatic condition a broader, less sharply defined, dividing line was found), and (4) the possible bilateral presence of the congenital condition.

Stieda's Shadows on the Inner Aspect of the Femoral Condyles.—Andreesen [28] studied 28 cases of Pellegrini-Stieda's disease. He divided them into three groups according to the roentgenographic changes shown on the inner femoral condyle: 1. Cases showing a simple striplike shadow along the inner femoral condyle. This was observed in 11 cases, in all of which there was a typical history of injury to the meniscus. 2. Cases showing a flat, irregular, shell-like shadow with a much decreased calcium content in comparison with the first group. This was observed in 8 patients, 3 of whom had a severe contusion on the inner side of the knee; the other 5 had severe twisting injuries. 3. Cases showing shadows much larger than usual, irregular and extending upward with apparent attachment to the condyle. In this group (9 patients) the injury to the knee was more severe; in 3 there was a tear of the cruciate ligament and in 2 a complete tear of the internal lateral ligament. The end-results were much poorer in this third group. As a cause of these shadows, the author suggested a tear with subsequent hemorrhage and later calcification at the attachment of the adductor magnus. In group 3 an additional injury to the adjacent periosteum was postulated. All patients were in the third to the fifth decade. Immobilization symptomatically for the original injury with surgical measures when indicated was the treatment used. Study of cases for as long as six years showed little change in these roentgen shadows. Symptoms, when present, were accounted for by derangement in function caused by the original injury.

Posttraumatic Painful Osteoporosis.—Fontaine and Herrmann [29] advocated sympathectomy in cases of traumatic osteoporosis, a form of treatment carried out in Lerichel's clinic since 1924. The condition usually involved the bones of the hand or foot, and followed either

27. Boyd, G. I.: Brit. J. Surg. **20**:455, 1933.
28. Andreesen, R.: Arch. f. klin. Chir. **174**:162, 1933.
29. Fontaine, R., and Herrmann, L. G.: Ann. Surg. **97**:26, 1933.

slight injuries (strains or sprains) or more extensive injuries (fractures or dislocations). It was characterized by: (1) loss of motor function of the extremity, (2) characteristic (osteoporotic) changes in the roentgenogram, (3) vasomotor disturbance and (4) pain. Twenty-two cases were reported, including 9 cases involving the bones of the wrist, 7 cases involving the bones of the ankle and 3 cases involving the bones of the shoulder joint.

Nature and Treatment of So-Called Tennis Elbow.—Hohmann,[30] from his studies of tennis elbow, concluded that the primary cause was a periosteal tear. In roentgenograms a thickening could usually be observed over the lateral epicondyle. For treatment in the early cases, rest was advocated, usually with a plaster cast including the hand, with no stretching of the spastic muscles about the elbow or forearm. Diathermy was given but no massage. In the chronic cases, operative treatment was advised. A curved incision was carried down to the bone over the external epicondyle, and the extensor muscles were then pushed distally from their attachment, in this way removing the pull of the muscles on the previously injured periosteal area. Good results were reported in 15 cases in which this operation was performed.

Glycine Treatment of Progressive Muscular Dystrophy.—Kostakow and Slauck [31] studied the action of glycine in 7 persons with progressive muscular dystrophy as well as in 4 normal persons. They concluded that glycine played a rôle in muscular physiology similar to phosphatase and lactic acid. In muscular dystrophy the nature of the disease consisted in the inability of the body to metabolize creatine. By the addition of glycine, the muscular metabolism was improved and creatine metabolism was made more nearly normal. Through glycine therapy, the authors felt that new therapeutic possibilities were presented for the patients with progressive muscular dystrophy.

Gas Gangrene and Its Treatment.—Effkemann [32] reviewed 53 cases of gas gangrene in which treatment was given at the Rudolf Virchow Hospital between 1928 and 1931. Thirty-four of the patients recovered, 16 with amputation; 19 died, 3 after amputation. Bacillus welchii was found in almost every case, usually in combination with other anaerobes. The local death of tissue, presence of nonpathogenic anaerobes, alkali content of the wound and poor hemostasis all aided in producing gas gangrene. In experimental animals the author was unable to produce gas gangrene with pure cultures of B. welchii when the wound was left open, even when earth was added; sewing the wound often led to

30. Hohmann, G.: München. med. Wchnschr. **80**:250 (Feb. 17) 1933.

31. Kostakow, S., and Slauck, A.: Deutsche med. Wchnschr. **59**:169 (Feb. 3) 1933.

32. Effkemann, G.: Arch. f. klin. Chir. **174**:1, 1933.

gas gangrene. Latent infections as shown in experimental animals might be activated by subsequent purulent infections. The best results were observed with large, repeated doses of a polyvalent serum. In addition, wide incision and packing with antiseptics were used. As antiseptics, solutions of potassium permanganate and surgical solution of chlorinated soda seemed best.

FRACTURES

Damage to the Knee Joint from Long-Continued Traction in Fractures of the Thigh.—Felsenreich [33] analyzed two groups of femoral fractures each comprising 30 cases. The first group was treated by traction applied through the tuberosities of the tibiae. The second group was treated by traction through the femoral condyles. The author's interest lay in the consideration of symptoms of the knee joint which so often followed long-continued traction through the joint. In 5 of the 30 patients on whom tibial traction was employed severe "traction injuries" developed, necessitating manipulation. At these attempts adhesions were demonstrable, particularly in the suprapatellar pouch. Only 3 of the 5 did well. The author stated that instability of the knee did not develop in this group, but that definite limitation of motion had appeared. The articular capsule was stretched; the delicate synovial lining also was stretched. Inflammatory evidences of pain and effusion appeared rapidly, and in a few weeks extensive adhesions were present in the joint. For these reasons Felsenreich felt that traction through the tibial tuberosities was undesirable and should never be persisted in more than from three to four weeks, even in cases in which no alternative to traction was advisable. He advised condylar traction wherever possible, and open reduction, when necessary, as the lesser of two evils.

[Ed. Note.—The author, in attributing these disabilities to traction, seems to be overlooking the influence of prolonged immobilization.]

Treatment of Patellar Fractures and Posttraumatic Arthritis.—Of 57 patients with patellar fractures with separation of the fragments, 17 were treated conservatively and 40 were operated on by Frederick.[34] In 90 per cent of the cases in which operation was performed, normal or almost normal function was obtained, compared to less than 60 per cent of normal function in the nonoperative groups. In more than 50 per cent of the operative group, the result was perfect. Bony healing occurred proportionately three times as often in the operative group as in the nonoperative group. Arthritis appeared twice as often in the nonoperative as in the operative group. Frederick believed the

33. Felsenreich, F.: Arch. f. klin. Chir. **174**:667, 1933.
34. Frederick, R.: Arch. f. klin. Chir. **174**:747, 1933.

causes of the arthritis to be: (1) trauma, (2) hemarthrosis, (3) long immobilization of the joint and (4) poor union of the fracture.

Operation for Fracture of the Patella.—Ober [35] reported on a single case of transverse fracture of the patella which was repaired with a portion of the quadriceps tendon. The midportion of the quadriceps tendon was divided transversely approximately 4 inches above the superior border of the patella and split longitudinally, and the two pieces of tendon were dissected free down to the patella. These two tendinous strips were then passed through drill holes in the patella and sewed to the ligamentum patellae. The patella united solidly, and the patient obtained 85 per cent of flexion in approximately eight months' time.

Fractures of the Head and Neck of the Radius.—Fourteen cases of fracture of the proximal end of the radius in children were reported by Bohrer.[36] These cases from the Children's Fracture Clinic at Bellevue Hospital were seen during the past ten years and represented 3 per cent of all of the fractures about the elbow joint. From a study of these cases the author concluded that fractures of the head and neck of the radius in children should be treated conservatively unless there was marked displacement of the fragments; with marked displacement, early operation with replacement was preferable to resection. If resection was done, about 50 per cent would present synostosis of the radius and ulna several months after operation. Of 5 children operated on, 2 had full function permanently; 3 had complete function when discharged from the hospital, but over a period of several months rotation was lost because of productive periostitis followed by synostosis of the radius and ulna. Of the 9 patients treated conservatively, 3 had severe injuries with displacement or comminution of the head of the radius, synostosis developed in 2 with loss of rotation, and 1 recovered complete function. The remaining 6, with slight trauma, recovered complete function.

[ED. NOTE.—This article gives an excellent discussion of the subject. Operative treatment is less frequently indicated for children than for adults. If operation is to be done, it must be done early.]

End-Results of Carpal Scaphoid Fractures.—One hundred and seven cases of fracture of the carpal scaphoid were reported from the surgical dispensary of the Episcopal Hospital in Philadelphia by Snodgrass.[37] Ninety-five of the patients were males and 12 were females. The end-results were determined in 61 cases, in 48 of which roentgenographic studies were made. In 40 cases the final result was listed as good,

35. Ober, F. R.: J. Bone & Joint Surg. **14**:640, 1932.
36. Bohrer, J. V.: Ann. Surg. **97**:204, 1933.
37. Snodgrass, L. E.: Ann. Surg. **97**:209, 1933.

in 10 moderately good and in 11 poor. Five of the 61 patients had been operated on, with poor results in 3 and good results in 2.

[ED. NOTE.—A more complete analysis of these cases would be of interest. From this series of cases the conservative type of treatment is shown to be the best.]

Late Results of Separation of Epiphyses.—Ireland [38] examined 18 patients with 19 epiphyseal separations, from seventy-four days to seven and one-half years after the original injury. Sixteen of these lesions were due to trauma and 3 to scurvy. Eleven patients were treated conservatively by closed reduction. Of these, 1 had shortening and 1 had lengthening as measured in roentgenograms; 2 had osseous union of the epiphysis to the shaft; 1 had deformity, and 1 had poor function, but none had arthritis. Two patients with 3 epiphyseal separations due to scurvy were treated by simple rest in bed without splints, but were given antiscorbutic food and medication. One had shortening and deformity, but in neither was there osseous union of the epiphysis to the shaft, impaired function or arthritis. Five patients were treated by open operation. All of these had subsequent shortening as measured by roentgenograms, and 4 showed shortening by external measurements; 1 had osseous union of the epiphysis to the shaft, and 1 had a resulting deformity, poor function and arthritis after removal of the epiphysis.

Osteosynthesis for Fracture of the Femoral Neck According to Sven Johannson.—Krauss [39] considered Johannson's modification of Smith-Petersen's [40] procedure of nailing the fractured femoral neck a distinct advance. Johannson inserted a Kirschner wire through the site of fracture. The position of the wire was then checked by roentgenograms, the table being specially fitted for this purpose. After the Kirschner wire had been satisfactorily placed, a special nail with a hole in its longitudinal axis was threaded on the wire and driven into the femoral neck over the guide wire. The Kirschner wire was then withdrawn. This procedure obviated the necessity for a long incision.

[ED. NOTE.—This is an ingenious improvement in technic which may later prove to be useful. There is always the danger that the fracture may appear to be satisfactorily reduced in anteroposterior roentgenograms while roentgenograms in the lateral plane will show that the fracture is not reduced.]

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38. Ireland, J.: Ann. Surg. **97**:189, 1933.

39. Krauss, F.: Zentralbl. f. Chir. **60**:864, 1933.

40. Smith-Petersen, M. N.; Cave, E. F., and Vangorder, G. W.: Intracapsular Fractures of the Neck of the Femur: Treatment by Internal Fixation, Arch. Surg. **23**:715 (Nov.) 1931.

Slipping of Epiphysis of the Head of the Femur.—That some cases of slipped upper femoral epiphysis in the adolescent were due to renal rickets was the opinion of Brailsford,[41] who concluded that this condition could be diagnosed roentgenographically by an increase of the density of the metaphyseal periphery of the epiphysis, some increase in the breadth of the metaphysis, and a "woolliness" of the extremity of the diaphysis. The urine of such patients contained albumin. Under suitable treatment, consolidation took place within a month.

Results in Treatment of Fractures of the Thigh.—Brandt[42] reviewed 440 fractures of the thigh observed in Magnus' clinic in Bochum between 1925 and 1929. Seven of the patients died, 2 from hemorrhage, and 5 from embolic complications from two to seventeen days after the injury. Compound fractures were observed in 46 cases, or 10.2 per cent. They were divided into three groups anatomically: (1) fractures proximal to the trochanters, 110; (2) fractures of the femoral diaphysis, 299; (3) supracondylar and condylar fractures, 31. Treatment consisted usually of extension with the hip in midabduction and with slight flexion of the hip and knee. Skeletal traction on the head of the tibia was carried out in 369 cases, with infection resulting at the site of traction only once. No subsequent instability was observed in the knee joint. Extension was continued until consolidation of the fracture had occurred. Open reduction was attempted rarely. Nailing was done in articular fractures of the condyles. When it was necessary, position was maintained by wire traction about the fragments. This wire was removed in from three to four weeks. Light extension was the usual treatment in fractures of the femoral neck; 73.5 per cent of the cases healed without shortening. (Tables showing the end-results were not given.)

Fractures of the Spinous Process.—Bofinger[43] collected reports of 16 cases of fracture of the spinous processes of the cervical and dorsal vertebrae. In most instances the patient remained at work, and later when a physician was consulted the correct diagnosis was rarely made. The clinical signs were tenderness and pain in the lower cervical or upper dorsal region with occasional localized swelling. Lateral roentgenograms rarely showed fractures of the spinous processes, but anteroposterior roentgenograms showed irregularities and displacements instead of the normal round or oval shadows of the spinous processes. The author believed that the fracture was due to muscular pull. Local muscular fatigue seemed to be the chief predisposing cause.

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41. Brailsford, J. F.: Lancet **1**:16, 1933.
42. Brandt, K. D.: Ztschr. f. Chir. **239**:294, 1933.
43. Bofinger: München. med. Wchnschr. **80**:146 (Jan. 27) 1933.

Treatment and Evaluation of Vertebral Fractures.—Schleipen [44] reviewed 109 cases of vertebral fracture observed at Freiburg in the past ten years. Extension was applied in fractures of the cervical spine. In the remaining cases the patient was kept on a hard bed until healing had occurred. Massage was begun in the second week. Sitting with support was permitted in four weeks. Standing was permitted in from seven to nine weeks. Ossification to neighboring vertebrae and arthritis of the vertebral joints were commonly seen in the region of the fracture. The mortality was 35 per cent in cervical fractures; 17 per cent in thoracic fractures, and 3.6 per cent in lumbar fractures. Death was usually due to injury to the spinal cord. Two deaths were due to fat emboli. Only 10 patients were completely without pain after two years. Normal spinal motion was found in only 23. The best results were observed in the cases in which motion was resumed early without atrophy of the spinal muscles.

[Ed. Note.—The bibliography of the author showed that he was familiar with the methods used in America for decompression; but apparently they were not used in this clinic. One has only to read the results reported in this article to appreciate the value of modern methods which bring about the reduction and fixation of such vertebral fractures.]

RESEARCH

Healing of Bone and Cartilage After Sympathectomy.—Key and Moore,[45] using cats, produced fractures in the bones of the extremities and defects in the articular cartilage. Approximately one or two months later sympathectomies were performed, and while dilatation of the blood vessels was produced, there was no demonstrable effect on the rate of healing of the fractures or repair of the cartilage as compared to similar injuries in control animals.

Influencing Growth and Regeneration of the Bone.—Boeminghaus [46] studied the effect of the local and systemic applications of various substances on regeneration and growth of the bone in young dogs. He found that regeneration of the bone could not be influenced appreciably by intensive feeding of vitamins and calcium-rich food substances, by local hyperemia, by local injections of solutions of isotonic potassium or calcium chloride or through the use of anterior pituitary extract, provided the animals were in good health. The author concluded that in the organism that was not diseased osseous regeneration and growth proceeded at an optimum without local or systemic stimulation.

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44. Schleipen, C.: Deutsche Ztschr. f. Chir. **238**:618, 1933.

45. Key, J. A., and Moore, R. M.: Healing of Fractures, of Defects in Bone and of Defects in Cartilage After Sympathectomy, Arch. Surg. **26**:272 (Feb.) 1933.

46. Boeminghaus, H.: Deutsche Ztschr. f. Chir. **238**:684, 1933.

Effect of Viosterol on the Periosteum in Experimental Fractures.—Grauer [47] found that viosterol in therapeutic doses caused stimulation of the osteogenic layer of the periosteum in experimental fractures in the guinea-pig, while overdosage produced a condition simulating osteitis fibrosa with retardation in repair and decalcification of the bone.

The Effect of a Diet Low in Calcium on the Breaking Strength of Healing Fractures.—McKeown and co-workers [48] found that a diet low in calcium had little effect on the normal breaking strength of unfractured fibulae or of healing fractures in albino rats. They attributed this to an increase in the organic elements of the bone, substituting increased pliability for a decrease in the calcium content of the bone. They concluded that phosphorus was of more importance to the strength of healing fractures than calcium.

Experimental Studies on Tuberculosis of the Bone.—Mandelstamm,[49] in experimentally produced tuberculosis of the bones, found tubercles always about the larger blood vessels whether infection was produced by intracardial injection, subcutaneous injection or intra-articular injection. The epiphyses showed a much greater tendency to the disease than the diaphyses. There seemed to be a local difference in the resistance of the tissue in various parts of a bone. Tubercles did not develop with equal frequency in different parts of the bone. There was no caseation in the bone marrow of the diaphysis, while this was frequently observed in the epiphyses. In the fatty marrow no tubercles developed. In rabbits intraperitoneal injections (lymphatic absorption) of bovine tubercle bacilli produced a generalized infection and death in about two months with numerous tuberculous foci in the bones and joints.

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47. Grauer, R. C.: The Effect of Viosterol on the Periosteum in Experimental Fractures, Arch. Surg. **25**:1035 (Dec.) 1932.

48. McKeown, R. K.; Harvey, S. C., and Lumsden, R. W.: Breaking Strength of Healing Fractured Fibulae of Rats: Observations on Low Calcium Diet, Arch. Surg. **25**:1011 (Dec.) 1932.

49. Mandelstamm, M.: Beitr. z. klin. d. Tuberk. **82**:98, 1933.